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(74) Agents: MAKI, David, J. et al.; Seed and Berry LLP, 6300 Columbia, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).

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(71) Applicant: CORIXA CORPORATION [US/US]; Suite 200, 1124 Columbia Street, Seattle, WA 98104 (US).

(72) Inventors: DILLON, Davin, Clifford; 21607 N.E. 24th Street, Redmond, WA 98053 (US). HARLOCKER, Susan, Louise; 6203 20th Avenue N.W., Seattle, WA 98107 (US). YUQIU, Jiang; 5001 South 232nd Street, Kent, WA 98032 (US). XU, Jiangchun; 15805 S.E. 43rd Place, Bellevue, WA 98006 (US). MITCHAM, Jennifer, Lynn; 16677 Northeast 88th Street, Redmond, WA 98052 (US).

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#### (57) Abstract

Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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## COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER

#### **TECHNICAL FIELD**

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides comprising at least a portion of a prostate tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of such cancers.

#### BACKGROUND OF THE INVENTION

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

#### SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present

invention provides polypeptides comprising at least a portion of a prostate tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and (c) complements of any of the sequence of (a) or (b). In certain specific embodiments, such a polypeptide comprises at least a portion, or variant thereof, of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and a non-specific immune response enhancer.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a non-specific immune response enhancer.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic

kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

#### BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate tumor polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate tumor polypeptide P502S. In each case, the number of  $\gamma$ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate tumor polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate tumor antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target rations as indicated.

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SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

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SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 SEQ ID NO: 115 is the determined cDNA sequence for P89 SEQ ID NO: 116 is the determined cDNA sequence for P90 SEQ ID NO: 117 is the determined cDNA sequence for P92 SEQ ID NO: 118 is the determined cDNA sequence for P95 SEQ ID NO: 119 is the determined cDNA sequence for P98 SEQ ID NO: 120 is the determined cDNA sequence for P102 SEQ ID NO: 121 is the determined cDNA sequence for P110 SEQ ID NO: 122 is the determined cDNA sequence for P111 SEQ ID NO: 123 is the determined cDNA sequence for P114 SEO ID NO: 124 is the determined cDNA sequence for P115 SEQ ID NO: 125 is the determined cDNA sequence for P116 SEQ ID NO: 126 is the determined cDNA sequence for P124 SEQ ID NO: 127 is the determined cDNA sequence for P126 SEQ ID NO: 128 is the determined cDNA sequence for P130 SEQ ID NO: 129 is the determined cDNA sequence for P133 SEQ ID NO: 130 is the determined cDNA sequence for P138 SEQ ID NO: 131 is the determined cDNA sequence for P143 SEQ ID NO: 132 is the determined cDNA sequence for P151 SEQ ID NO: 133 is the determined cDNA sequence for P156 SEQ ID NO: 134 is the determined cDNA sequence for P157 SEQ ID NO: 135 is the determined cDNA sequence for P166 SEQ ID NO: 136 is the determined cDNA sequence for P176 SEQ ID NO: 137 is the determined cDNA sequence for P178 SEQ ID NO: 138 is the determined cDNA sequence for P179 SEQ ID NO: 139 is the determined cDNA sequence for P185 SEQ ID NO: 140 is the determined cDNA sequence for P192 SEQ ID NO: 141 is the determined cDNA sequence for P201 SEQ ID NO: 142 is the determined cDNA sequence for P204 SEQ ID NO: 143 is the determined cDNA sequence for P208 SEQ ID NO: 144 is the determined cDNA sequence for P211 SEQ ID NO: 145 is the determined cDNA sequence for P213 SEQ ID NO: 146 is the determined cDNA sequence for P219 SEQ ID NO: 147 is the determined cDNA sequence for P237 SEQ ID NO: 148 is the determined cDNA sequence for P239 SEQ ID NO: 149 is the determined cDNA sequence for P248

SEQ ID NO: 150 is the determined cDNA sequence for P251 SEQ ID NO: 151 is the determined cDNA sequence for P255 SEQ ID NO: 152 is the determined cDNA sequence for P256 SEQ ID NO: 153 is the determined cDNA sequence for P259 SEQ ID NO: 154 is the determined cDNA sequence for P260 SEQ ID NO: 155 is the determined cDNA sequence for P263 SEQ ID NO: 156 is the determined cDNA sequence for P264 SEQ ID NO: 157 is the determined cDNA sequence for P266 SEQ ID NO: 158 is the determined cDNA sequence for P270 SEQ ID NO: 159 is the determined cDNA sequence for P272 SEQ ID NO: 160 is the determined cDNA sequence for P278 SEQ ID NO: 161 is the determined cDNA sequence for P105 SEQ ID NO: 162 is the determined cDNA sequence for P107 SEQ ID NO: 163 is the determined cDNA sequence for P137 SEQ ID NO: 164 is the determined cDNA sequence for P194 SEQ ID NO: 165 is the determined cDNA sequence for P195 SEQ ID NO: 166 is the determined cDNA sequence for P196 SEQ ID NO: 167 is the determined cDNA sequence for P220 SEQ ID NO: 168 is the determined cDNA sequence for P234 SEQ ID NO: 169 is the determined cDNA sequence for P235 SEQ ID NO: 170 is the determined cDNA sequence for P243 SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1 SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1 SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2 SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6 SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13 SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13 SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14 SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14 SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-4736 SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-4738 SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-4741 SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-4744 SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-4774 SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-4781 SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-4785 SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-4787

SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-4796 SEQ ID NO: 188 is the determined extended cDNA sequence for 11-4807 SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810 SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811 SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-4876 SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-4884 SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-4896 SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-4761 SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-4762 SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-4766 SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770 SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771 SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-4772 SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-4309 SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-4278 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-4288 SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-4283 SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-4304 SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-4296 SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-4280 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev SEQ ID NO: 223 is the determined cDNA sequence for P509S

SEQ ID NO: 224 is the determined cDNA sequence for P510S
SEQ ID NO: 225 is the determined cDNA sequence for P703DE5
SEQ ID NO: 226 is the determined cDNA sequence for 9-A11
SEQ ID NO: 227 is the determined cDNA sequence for 8-C6
SEQ ID NO: 228 is the determined cDNA sequence for 8-H7
SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13
SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14
SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23
SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24
SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25
SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30
SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34
SEQ ID NO: 236 is the determined cDNA sequence for PTPN35
SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36
SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38
SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39
SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40
SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41
SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42
SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51
SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56
SEQ ID NO: 247 is the determined cDNA sequence for PTPN64
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76
SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84
SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88
SEQ ID NO: 256 is the determined cDNA sequence for JP1F1
SEQ ID NO: 257 is the determined cDNA sequence for JP1F2
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2

SEQ ID NO: 261 is the determined cDNA sequence for JP1D3 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4 SEQ ID NO: 263 is the determined cDNA sequence for JP1F5 SEQ ID NO: 264 is the determined cDNA sequence for JP1E6 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6 SEQ ID NO: 266 is the determined cDNA sequence for JP1B5 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6 SEQ ID NO: 268 is the determined cDNA sequence for JP1E8 SEQ ID NO: 269 is the determined cDNA sequence for JP1D7 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9 SEQ ID NO: 271 is the determined cDNA sequence for JP1C10 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12 SEQ ID NO: 274 is the determined cDNA sequence for JP1E12 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11 SEQ ID NO: 276 is the determined cDNA sequence for JP1C11 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12 SEQ ID NO: 278 is the determined cDNA sequence for JP1B12 SEQ ID NO: 279 is the determined cDNA sequence for JP1A12 SEQ ID NO: 280 is the determined cDNA sequence for JP8G2 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2 SEQ ID NO: 283 is the determined cDNA sequence for JP8A3 SEQ ID NO: 284 is the determined cDNA sequence for JP8A4 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3 SEQ ID NO: 286 is the determined cDNA sequence for JP8G4 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6 SEQ ID NO: 288 is the determined cDNA sequence for JP8D6 SEQ ID NO: 289 is the determined cDNA sequence for JP8F5 SEQ ID NO: 290 is the determined cDNA sequence for JP8A8 SEQ ID NO: 291 is the determined cDNA sequence for JP8C7 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7 SEQ ID NO: 293 is the determined cDNA sequence for P8D8 SEQ ID NO: 294 is the determined cDNA sequence for JP8E7 SEQ ID NO: 295 is the determined cDNA sequence for JP8F8 SEQ ID NO: 296 is the determined cDNA sequence for JP8G8 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10

SEQ ID NO: 298 is the determined cDNA sequence for JP8C10 SEQ ID NO: 299 is the determined cDNA sequence for JP8E9 SEQ ID NO: 300 is the determined cDNA sequence for JP8E10 SEQ ID NO: 301 is the determined cDNA sequence for JP8F9 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9 SEQ ID NO: 303 is the determined cDNA sequence for JP8C12 SEQ ID NO: 304 is the determined cDNA sequence for JP8E11 SEQ ID NO: 305 is the determined cDNA sequence for JP8E12 SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12 SEQ ID NO: 307 is the determined cDNA sequence for P711P SEQ ID NO: 308 is the determined cDNA sequence for P712P SEQ ID NO: 309 is the determined cDNA sequence for CLONE23 SEQ ID NO: 310 is the determined cDNA sequence for P774P SEQ ID NO: 311 is the determined cDNA sequence for P775P SEQ ID NO: 312 is the determined cDNA sequence for P715P SEQ ID NO: 313 is the determined cDNA sequence for P710P SEQ ID NO: 314 is the determined cDNA sequence for P767P SEQ ID NO: 315 is the determined cDNA sequence for P768P SEQ ID NO: 316-325 are the determined cDNA sequences of previously isolated genes SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5 SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5 SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26 SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26 SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23 SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23 SEQ ID NO: 332 is the determined full length cDNA sequence for P509S SEQ ID NO: 333 is the determined extended cDNA sequence for P707P (also referred to as 11-C9) SEQ ID NO: 334 is the determined cDNA sequence for P714P SEQ ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-F3) SEQ ID NO: 336 is the predicted amino acid sequence for P705P SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10 SEQ ID NO: 338 is the amino acid sequence of the peptide p5 SEQ ID NO: 339 is the predicted amino acid sequence of P509S SEQ ID NO: 340 is the determined cDNA sequence for P778P

SEQ ID NO: 341 is the determined cDNA sequence for P786P SEQ ID NO: 342 is the determined cDNA sequence for P789P

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SEQ ID NO: 343 is the determined cDNA sequence for a clone showing homology to Homo sapiens MM46 mRNA

SEQ ID NO: 344 is the determined cDNA sequence for a clone showing homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA

SEQ ID NO: 345 is the determined cDNA sequence for a clone showing homology to Homo sapiens mRNA for E-cadherin

SEQ ID NO: 346 is the determined cDNA sequence for a clone showing homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)

SEQ ID NO: 347 is the determined cDNA sequence for a clone showing homology to Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2).

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to Human mRNA for proteosome subunit p40

SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEQ ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ ID

NO: 366.

SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ ID

NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ ID

NO: 375.

SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

SEQ ID NO: 385 is the cDNA sequence for CGI-82.

SEQ ID NO:386 is the cDNA sequence for 23320.

SEQ ID NO:387 is the cDNA sequence for CGI-69.

SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO:389 is the cDNA sequence for 23379.

SEQ ID NO:390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.

SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553.

SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567.

SEQ ID NO:412 is the cDNA sequence for 22568.

SEQ ID NO:413 is the cDNA sequence for 22570.

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SEQ ID NO:414 is the cDNA sequence for 22571.

SEQ ID NO:415 is the cDNA sequence for 22572.

SEQ ID NO:416 is the cDNA sequence for 22573.

SEQ ID NO:417 is the cDNA sequence for 22573.

SEQ ID NO:418 is the cDNA sequence for 22575.

SEQ ID NO:419 is the cDNA sequence for 22580.

SEQ ID NO:420 is the cDNA sequence for 22581.

SEQ ID NO:421 is the cDNA sequence for 22582.

SEQ ID NO:422 is the cDNA sequence for 22583.

SEQ ID NO:423 is the cDNA sequence for 22584.

SEQ ID NO:424 is the cDNA sequence for 22585.

SEQ ID NO:425 is the cDNA sequence for 22586.

SEQ ID NO:426 is the cDNA sequence for 22587.

SEQ ID NO:427 is the cDNA sequence for 22588.

SEQ ID NO:428 is the cDNA sequence for 22589.

SEQ ID NO:429 is the cDNA sequence for 22590.

SEQ ID NO:430 is the cDNA sequence for 22591.

SEQ ID NO:431 is the cDNA sequence for 22592.

SEQ ID NO:432 is the cDNA sequence for 22593.

SEQ ID NO:433 is the cDNA sequence for 22594.

SEQ ID NO:434 is the cDNA sequence for 22595.

SEQ ID NO:435 is the cDNA sequence for 22596.

SEQ ID NO:436 is the cDNA sequence for 22847.

SEQ ID NO:437 is the cDNA sequence for 22848.

SEQ ID NO:438 is the cDNA sequence for 22849.

SEQ ID NO:439 is the cDNA sequence for 22851.

SEQ ID NO:440 is the cDNA sequence for 22852.

SEQ ID NO:441 is the cDNA sequence for 22853.

SEQ ID NO:442 is the cDNA sequence for 22854. SEQ ID NO:443 is the cDNA sequence for 22855.

SEQ ID NO:444 is the cDNA sequence for 22856.

SEQ ID NO:445 is the cDNA sequence for 22857. SEQ ID NO:446 is the cDNA sequence for 23601.

SEQ ID NO:447 is the cDNA sequence for 23602.

SEQ ID NO:448 is the cDNA sequence for 23605.

SEQ ID NO:449 is the cDNA sequence for 23606.

SEQ ID NO:450 is the cDNA sequence for 23612.

SEQ ID NO:451 is the cDNA sequence for 23614.

SEQ ID NO:452 is the cDNA sequence for 23618.

SEQ ID NO:453 is the cDNA sequence for 23622.

SEQ ID NO:454 is the cDNA sequence for folate hydrolase.

SEQ ID NO:455 is the cDNA sequence for LIM protein.

SEQ ID NO:456 is the cDNA sequence for a known gene.

SEQ ID NO:457 is the cDNA sequence for a known gene.

SEQ ID NO:458 is the cDNA sequence for a previously identified gene.

SEQ ID NO:459 is the cDNA sequence for 23045.

SEQ ID NO:460 is the cDNA sequence for 23032.

SEQ ID NO:461 is the cDNA sequence for 23054.

SEQ ID NOs:462-467 are cDNA sequences for known genes.

SEQ ID NOs:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

#### DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer. compositions described herein may include prostate tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a prostate tumor protein or a variant thereof. A "prostate tumor protein" is a protein that is expressed in prostate tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain prostate tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human prostate tumor proteins. Sequences of polynucleotides encoding certain tumor proteins, or portions thereof, are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Sequences of polypeptides comprising at least a portion of a tumor protein are provided in SEQ ID NOs:112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

#### PROSTATE TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a prostate tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a prostate tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a prostate tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a prostate tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native prostate tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50.

in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e., the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native prostate tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to

the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in a prostate tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using

standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding at least a portion of a prostate tumor protein are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Isolation of these

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polynucleotides is described below. Each of these prostate tumor proteins was overexpressed in prostate tumor tissue.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a prostate tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a prostate tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such

as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

#### PROSTATE TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a prostate tumor protein or a variant thereof, as described herein. As noted above, a "prostate tumor protein" is a protein that is expressed by prostate tumor cells. Proteins that are prostate tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences derived from

the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native prostate tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein.

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Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are

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E. coli, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into

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the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from Streptococcus pneumoniae, which synthesizes an N-acetyl-L-alanine amidase known as

amidase LYTA (encoded by the LytA gene; Gene 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of E. coli C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see Biotechnology 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

#### BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a prostate tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, urine and/or tumor biopsies) from

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patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient

time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and

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thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

#### T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a prostate tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the CEPRATE™ system, available from CellPro Inc., Bothell WA (*see also* U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a prostate tumor polypeptide, polynucleotide encoding a prostate tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience

(Greene 1998)). T cells that have been activated in response to a prostate tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Prostate tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a prostate tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

### PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998,

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and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or

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preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the OS21 is

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quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (i.e., a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects per se and/or to be immunologically compatible with the receiver (i.e., matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-

surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a prostate tumor protein (or portion or other variant thereof) such that the prostate tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that

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provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

#### **CANCER THERAPY**

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8+ cytotoxic T lymphocytes and CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein

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may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to nonvaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such

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a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a prostate tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding

agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10  $\mu$ g, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred

embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4+ and/or CD8+ T cells isolated from a patient is incubated with a prostate tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with prostate tumor polypeptide (e.g., 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostate tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8+ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a prostate tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the prostate tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers

comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375 and 381. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

#### DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a prostate tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a prostate tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

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### **EXAMPLES**

### **EXAMPLE 1**

### ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A\* RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A\* RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the Notl/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with Notl. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/Notl site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained  $1.64 \times 10^7$  independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained  $3.3 \times 10^6$  independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara et al. (Blood, 84:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 µg) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 µl of

 $H_2O$ , heat-denatured and mixed with 100  $\mu$ l (100  $\mu$ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50  $\mu$ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23  $\mu$ l  $H_2O$  to form the driver DNA.

To form the tracer DNA, 10 μg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H<sub>2</sub>O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H<sub>2</sub>O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK\* (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human

autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12. This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to R. norvegicus mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted

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amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and

prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D.1-4278, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

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Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339.

# EXAMPLE 2 DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate tumor polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that

F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancrease, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression

in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis et al. (Proc. Natl. Acad. Sci. USA 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

### **EXAMPLE 3**

ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' E. coli (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated

and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the microarray technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX 23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold overexpression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues.

Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

### EXAMPLE 4 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following

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lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

### **EXAMPLE 5**

### FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat norvegicus cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to G. gallus dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 10 (SEQ ID NO: 340-349) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350-365.

### EXAMPLE 6 PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2.1 (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., Proc. Natl. Acad. Sci. USA 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100µg of P2S#12 and 120µg of an I-Ab binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6 x 106 cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10<sup>-5</sup> M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of  $7\mu g/ml$  dextran sulfate and  $25\mu g/ml$  LPS for 3 days). Six days later, cells (5 x 105/ml) were restimulated with 2.5 x 106/ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, Science 258:815-818, 1992) and 3 x 106/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x  $10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x  $10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were

restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2.1 expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2.1 molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, J. Immunol., 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200  $\mu g/ml$ were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2.1 were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5μg of P1S #10 and 120μg of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2μ g/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). Six days later cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 10<sup>6</sup>/ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3 x 10<sup>6</sup>/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly

basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

## EXAMPLE 7 ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE TUMOR POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8<sup>+</sup> T cells were primed in vitro to the P2S-12 peptide (SEQ ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (Critical Reviews in Immunology 18:65-75, 1998). The resulting CD8+ T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a γ-interferon ELISPOT assay (see Lalvani et al., J. Exp. Med. 186:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on 104 fibroblasts in the presence of 3  $\mu$ g/ml human  $\beta_2$ -microglobulin and 1  $\mu$ g/ml P2S-12 peptide or control E75 In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/neu. Prior to the assay, the fibroblasts were treated with 10 ng/ml γ-interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a γ-interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of y-interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of y-interferon spots with increasing numbers of T

cells on fibroblasts transduced to express the P502S gene but not the HER-2/neu gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

## EXAMPLE 8 PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION WITH A PROSTATE ANTIGEN

The prostate tumor antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg VR10132-P501S either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed A2-restricted CTL epitope.

### **EXAMPLE 9**

## GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH PROSTATE TUMOR ANTIGEN

Using *in vitro* whole-gene priming with P501S-retrovirally transduced autologous fibroblasts (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon-γ ELISPOT analysis as described above. Using a panel of HLA-mismatched fibroblast lines transduced with P501S, these CTL lines were shown to be restricted HLA-A2 class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3 μg/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and

priming cultures were initiated using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon-γ when stimulated with P501S-transduced autologous fibroblasts. The P501S-specific activity could be sustained by the continued stimulation of the cultures with P501S-transduced fibroblasts in the presence of IL-15. A panel of HLA-mismatched fibroblast lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon-γ in an ELISPOT assay, the P501S specific response was shown to be restricted by HLA-A2. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

### **EXAMPLE 10**

### IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN A PROSTATE TUMOR ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2 transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of P703P transduced target cells expressing either HLA-A2Kb or HLA-A2. Specifically, HLA-A2 transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with p5 peptide and cultured with GM-CSF and IL-4 together with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis

with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated.

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# EXAMPLE 11 EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate tumor and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach).

## EXAMPLE 12 ELICITATION OF PROSTATE TUMOR ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate tumor antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8<sup>+</sup> cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to

express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxity assays (<sup>51</sup>Cr release) and interferon-gamma production (Interferon-gamma Elispot; *see* above and Lalvani et al., *J. Exp. Med. 186*:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

# EXAMPLE 13 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

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Table I
Summary of Prostate Tumor Antigens

Known Genes	Previously identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	12 110.370)
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang(23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	

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transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate

tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was overexpressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

## EXAMPLE 14 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate tumor antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA 95*:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups, Plus (normal prostate and prostate tumor libraries, and breast cell lines, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

<u>Table II</u>

<u>Prostate cDNA Libraries and ESTs</u>

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones found in the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones found in the Plus, Minus and Other group libraries, but the expression in the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones found in Plus, Minus and Other group libraries, but the expression in the Plus group is higher than the expression in the Minus group. This analysis identified 4,345 breast clusters (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

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<u>Table III</u>

<u>Prostate Cluster Summary</u>

Туре	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	. 85	11
4	673	0
Total	4345	3172

The inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (i.e., the level in prostate tumor cDNA was at least three times the level in normal prostate cDNA) were identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NOs:401-453, with certain novel sequences shown in SEQ ID NOs:407, 413, 416-419, 422, 426, 427 and 450.

<u>Table IV</u>

<u>Prostate-tumor Specific Clones</u>

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P

403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57

439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

# EXAMPLE 15 FURTHER IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NOs:454-467. Of these sequences SEQ ID NOs:459-461 correspond to novel genes. The others (SEQ ID NOs:454-458 and 461-467) correspond to known sequences.

## EXAMPLE 16 FURTHER CHARACTERIZATION OF PROSTATE TUMOR ANTIGEN P710P

This Example describes the full length cloning of P710P.

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The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic ABI Sequencer. Four sequences were obtained, and are presented in SEQ ID NOs:468-471.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

### **CLAIMS**

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- 1. An isolated polypeptide comprising at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472;
- (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and
  - (c) complements of any of the sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotide sequences.
- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 339 and 383.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigenspecific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434.

435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.

- 5. An isolated polynucleotide encoding a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.
- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
- 7. An isolated polynucleotide comprising a sequence that hybridizes, under moderately stringent conditions, to a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector comprising a polynucleotide according to any one of claims 4-7.
- 10. A host cell transformed or transfected with an expression vector according to claim 9.
  - 11. An expression vector comprising a polynucleotide according claim 8.

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- 12. A host cell transformed or transfected with an expression vector according to claim 11.
- A pharmaceutical composition comprising a polypeptide according to 13. claim 1, in combination with a physiologically acceptable carrier.
- A vaccine comprising a polypeptide according to claim 1, in 14. combination with a non-specific immune response enhancer.
- A vaccine according to claim 14, wherein the non-specific immune 15. response enhancer is an adjuvant.
- A vaccine according to claim 14, wherein the non-specific immune 16. response enhancer induces a predominantly Type I response.
- A pharmaceutical composition comprising a polynucleotide according 17. to claim 4, in combination with a physiologically acceptable carrier.
- A vaccine comprising a polynucleotide according to claim 4, in 18. combination with a non-specific immune response enhancer.
- 19. A vaccine according to claim 18, wherein the non-specific immune response enhancer is an adjuvant.
- 20. A vaccine according to claim 18, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- An isolated antibody, or antigen-binding fragment thereof, that 21. specifically binds to a prostate tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472 or a complement of any of the foregoing polynucleotide sequences.

22. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 18, in combination with a physiologically acceptable carrier.

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- 23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.
- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 26. A vaccine according to claim 25, wherein the non-specific immune response enhancer is an adjuvant.
- 27. A vaccine according to claim 25, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.
- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 4, and thereby inhibiting the development of a cancer in the patient.
- 31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-binding fragment thereof according to claim 21, and thereby inhibiting the development of a cancer in the patient.

- 32. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 33. A method according to claim 32, wherein the antigen-presenting cell is a dendritic cell.
- 34. A method according to any one of claims 29-32, wherein the cancer is prostate cancer.
- 35. A fusion protein comprising at least one polypeptide according to claim 1.
- 36. A fusion protein according to claim 35, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 37. A fusion protein according to claim 35, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 38. A fusion protein according to claim 35, wherein the fusion protein comprises an affinity tag.
- 39. An isolated polynucleotide encoding a fusion protein according to claim 35.
- 40. A pharmaceutical composition comprising a fusion protein according to claim 32, in combination with a physiologically acceptable carrier.
- 41. A vaccine comprising a fusion protein according to claim 35, in combination with a non-specific immune response enhancer.
- 42. A vaccine according to claim 41, wherein the non-specific immune response enhancer is an adjuvant.

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- 43. A vaccine according to claim 41, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 44. A pharmaceutical composition comprising a polynucleotide according to claim 40, in combination with a physiologically acceptable carrier.
- 45. A vaccine comprising a polynucleotide according to claim 40, in combination with a non-specific immune response enhancer.
- 46. A vaccine according to claim 45, wherein the non-specific immune response enhancer is an adjuvant.
- 47. A vaccine according to claim 45, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 40 or claim 44.
- 49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 41 or claim 45.
- 50. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the prostate tumor protein from the sample.

51. A method according to claim 50, wherein the biological sample is blood or a fraction thereof.

- 52. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
- 53. A method for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and/or
- (iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii); under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.
- 54. An isolated T cell population, comprising T cells prepared according to the method of claim 53.
- 55. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 54.
- 56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

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- 57. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate;

- (b) cloning at least one proliferated cell; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
- 58. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 59. A method according to claim 58, wherein the binding agent is an antibody.
- 60. A method according to claim 59, wherein the antibody is a monoclonal antibody.

- 61. A method according to claim 58, wherein the cancer is prostate cancer.
- 62. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 63. A method according to claim 62, wherein the binding agent is an antibody.
- 64. A method according to claim 63, wherein the antibody is a monoclonal antibody.
- 65. A method according to claim 62, wherein the cancer is a prostate cancer.
- 66. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 67. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 68. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 69. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 70. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 71. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
  - 72. A diagnostic kit, comprising:
  - (a) one or more antibodies according to claim 21; and
  - (b) a detection reagent comprising a reporter group.

- 73. A kit according to claim 72, wherein the antibodies are immobilized on a solid support.
- 74. A kit according to claim 73, wherein the solid support comprises nitrocellulose, latex or a plastic material.
- 75. A kit according to claim 72, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.
- 76. A kit according to claim 72, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 77. An oligonucleotide comprising 10 to 40 nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotides.
- 78. A oligonucleotide according to claim 77, wherein the oligonucleotide comprises 10-40 nucleotides recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
  - 79. A diagnostic kit, comprising:
  - (a) an oligonucleotide according to claim 77; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

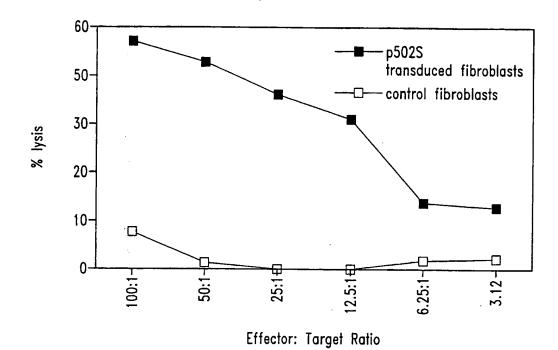


Fig. 1

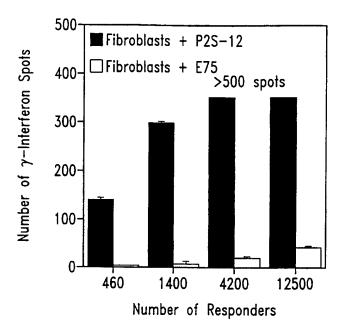


Fig. 2A

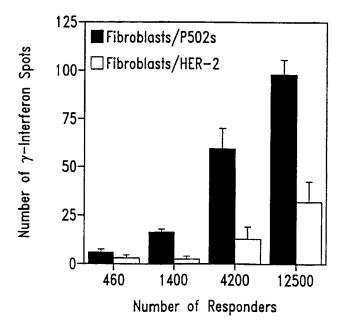
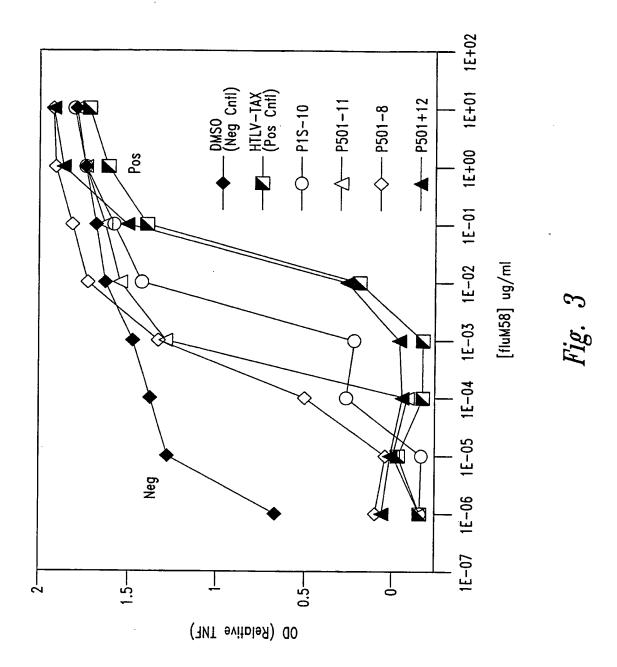


Fig. 2B

SUBSTITUTE SHEET (RULE 26)



SUBSTITUTE SHEET (RULE 26)

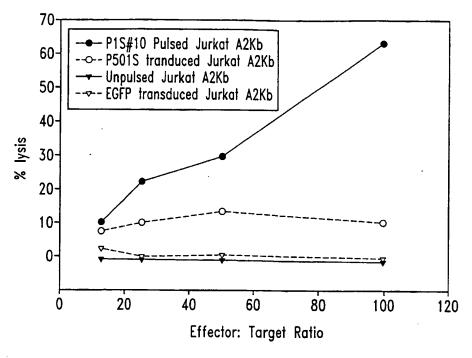
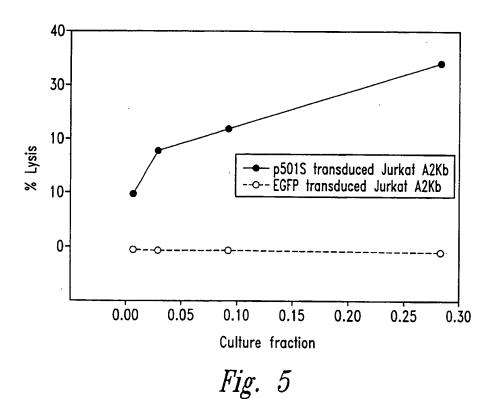
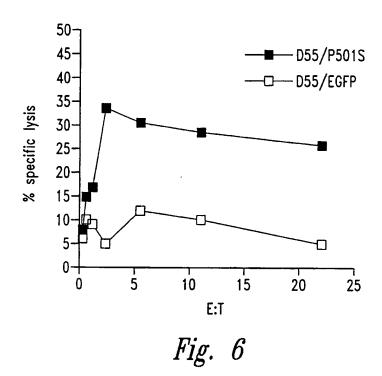
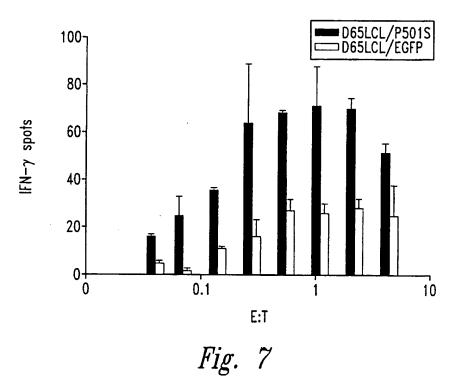


Fig. 4



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<110> Corixa Corporation

#### SEQUENCE LISTING

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       OF PROSTATE CANCER AND METHODS FOR THEIR USE
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      <140> PCT
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acceccaent nnacegetta caetttgeca gegeettane geeegeteee ttteneettt-
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teggaacact ggetgtetet gaagacttet egeteagttt cagtgaggae acacacaaag
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gngggcactg ggaagcctan atnaggccgt gagcanaaag aaggggagga tccactagtt
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teegetteet eneteantta ntecetnene teggteatte eggetgenge aaaceggtte
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qtcattanga nggctnaaaa ggccctgtta ngggtctggg ctnggtttta cccnacccat
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cnttatentn aaaggtnata aceneteeta tnateecace caatngnatt ceccaenenn
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                                                                        817
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teettteent tnagggttaa tnnegeettg geettneean ngteetnene ntttteennt
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gttnaaattg ttangeneee neennteeen ennennenan eeegaeeenn annttnnann
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```

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<213> Homo sapien

```
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gcacagggtg gcagcaaaaa aaccacttta ctttggcaca aacaaaaact ngggggggca
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accceggcac ceenangggg gttaacagga anengggnaa entggaacce aattnaggea
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ctgtgtggtg cagccctgtt ggcagtgggc atctgggtgt caatcqatqq qqcatccttt
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ctcatcgcag ccggcgttgt ggtcttagct ctaggtttcc tgggctgcta tggtgctaaq
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actgagagca agtgtgccct cgtgacgttc ttcttcatcc tcctcctcat cttcattgct
                                                                       420
gaggttgcaa tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctqacqt
                                                                        480
tgctggtaat gcctgccatc aanaaaagat tatgggttcc caggaanact tcactcaagt
                                                                        540
gttggaacac caccatgaaa gggctcaagt gctgtggctt cnnccaacta tacqqatttt
                                                                        600
gaagantcac ctacttcaaa gaaaanagtg cctttccccc atttctgttg caattgacaa
                                                                        660
acgtccccaa cacagccaat tgaaaacctg cacccaaccc aaangggtcc ccaaccanaa
                                                                       720
attnaaggg
                                                                       729
      <210> 14
      <211> 816
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(816)
      <223> n = A, T, C \text{ or } G
      <400> 14
tgctcttcct caaagttgtt cttgttgcca taacaaccac cataggtaaa gcgggcgcag
                                                                        60
tgttegetga aggggttgta gtaceagege gggatgetet cettgeagag teetgtgtet
                                                                       120
ggcaggtcca cgcagtgccc tttgtcactg gggaaatgga tgcgctggag ctcqtcaaaq
                                                                       180
ccactcgtgt atttttcaca ggcagcctcg tccgacgcgt cggggcagtt gggggtgtct
                                                                       240
tcacactcca ggaaactgtc natgcagcag ccattgctgc agcggaactg ggtqqqctqa
                                                                       300
cangigedag ageacactgg atggegeett tecatgnnan gggeeetgng ggaaagteee
                                                                       360
tganceccan anetgeetet caaangeece acettgeaca eeeegacagg etaqaatgga
                                                                       420
atottottoo ogaaaggtag tintiotigi igoocaanoo anoocontaa acaaactoti.
                                                                       480
gcanatctgc tccgnggggg tcntantacc ancgtgggaa aagaacccca ggcngcgaac
                                                                       540
caancttgtt tggatncgaa gcnataatct nctnttctgc ttggtggaca qcaccantna
                                                                       600
ctgtnnanct ttagncentg gteetentgg gttgnnettg aacetaaten cennteaact
                                                                       660
gggacaaggt aantngccnt cctttnaatt cccnancntn ccccctggtt tqqqqttttn
                                                                       720
cnenetecta ecceagaaan neegtgttee ecceeaacta ggggeenaaa cennttntte
                                                                       780
cacaaccctn ccccacccac gggttengnt ggttng
                                                                       816
      <210> 15
      <211> 783
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(783)
      <223> n = A,T,C \text{ or } G
```

```
<400> 15
ccaaggcctg ggcaggcata nacttgaagg tacaacccca ggaacccctg gtgctgaagg
                                                                        60
atgtggaaaa cacagattgg cgcctactgc ggggtgacac ggatgtcagg gtagagaga
                                                                       120
aagacccaaa ccaggtggaa ctgtggggac tcaaggaang cacctacctg ttccagctga
                                                                       180
cagtgactag ctcagaccac ccagaggaca cggccaacgt cacagtcact gtgctgtcca
                                                                       240
ccaagcagac agaagactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt
                                                                       300
teccaegetg gtactatgac eccaeggage agatetgeaa gagtttegtt tatggagget
                                                                       360
gcttgggcaa caagaacaac taccttcggg aagaagagtg cattctancc tgtcngggtg
                                                                       420
tgcaaggtgg gcctttgana ngcanctctg gggctcangc gactttcccc cagggcccct
                                                                       480
ccatggaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca
                                                                       540
ncaatggctg ctgcatcnac antttcctng aattgtgaca acacccccca ntgcccccaa
                                                                       600
ccctcccaac aaagcttccc tgttnaaaaa tacnccantt ggcttttnac aaacncccgg
                                                                       660
cncctccntt ttccccnntn aacaaagggc nctngcnttt gaactgcccn aacccnqqaa
                                                                       720
tetneenngg aaaaantnee eeceetggtt eetnnaance eeteenenaa anetneeece
                                                                       780
CCC
                                                                       783
      <210> 16
      <211> 801
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(801)
      <223> n = A,T,C or G
      <400> 16
gccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
                                                                        60
agctgattga agcaaccete tactttttgg tegtgageet tttgettggt geaggtttea
                                                                       120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                       180
aagtagggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
                                                                       240
atggtggtgt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca
                                                                       300
ggcactacca gcaacgtcag gaagtgctca gccattgtgg tgtacaccaa ggcgaccaca
                                                                       360
gcagctgcaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgagggca
                                                                       420
cacttgctct ccgtcttagc accatagcag cccangaaac.caagagcaaa.gaccacaacg
                                                                       480
ccngctgcga atgaaagaaa ntacccacgt tgacaaactg catggccact ggacgacagt
                                                                       540
tggcccgaan atcttcagaa aagggatgcc ccatcgattg aacacccana tgcccactgc
                                                                       600
cnacagggct geneenenen gaaagaatga gecattgaag aaggatente ntggtettaa
                                                                       660
tgaactgaaa ccntgcatgg tggcccctgt tcagggctct tggcagtgaa ttctganaaa
                                                                       720
aaggaacngc ntnagccccc ccaaangana aaacaccccc gggtgttgcc ctgaattggc
                                                                       780
ggccaaggan ccctgccccn g
                                                                       801
      <210> 17
      <211> 740
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(740)
      \langle 223 \rangle n = A,T,C or G
      <400> 17
gtgagagcca ggcgtccctc tgcctgccca ctcagtggca acacccggga gctgttttgt
```

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cettigtgga geeteageag ticeetetti cagaacteae igeeaagage cetqaacagg
                                                                        120
agccaccatg cagtgcttca gcttcattaa gaccatgatg atcctcttca atttgctcat
                                                                        180
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc
                                                                        240
ctttctgaag atcttcgggc cactgtcgtc cagtgccatg cagtttgtca acgtgggcta
                                                                        300
ettecteate geageeggeg ttgtggtett tgetettggt tteetggget getatqqtqe
                                                                        360
taagacggag agcaagtgtg ccctcgtgac gttcttcttc atcctcctcc tcatcttcat
                                                                        420
tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattcct
                                                                        480
gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc
                                                                        540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg
                                                                        600
gaattttgaa aganteneee taetteeaaa aaaaaanant tgeetttnee eeenttetgt
                                                                        660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa
                                                                        720
caaaaaant nnaagggttn
                                                                        740
      <210> 18
      <211> 802
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(802)
      \langle 223 \rangle n = A,T,C or G
      <400> 18
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                                                                        60
caaggtette cagetgeege acattaegea gggcaagage etecageaac actgeatatg
                                                                       120
ggatacactt tactttagca gccagggtga caactgagag gtgtcgaagc ttattcttct
                                                                       180
gagcctctgt tagtggagga agattccggg cttcagctaa gtagtcagcg tatgtcccat
                                                                       240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa
                                                                       300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat
                                                                       360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct
                                                                       420
ggttctgccc tgtcaccttc acttccgcac tcatcactgc actgagtgtg ggggacttgg
                                                                       480
getcaggatg tecagagaeg tggtteegee eeetenetta atgacaeegn ceanneaace
                                                                       540
gteggeteee geegantgng tregtegtne etgggteagg gtetgetgge enctacttge
                                                                       600
aancttcgtc nggcccatgg aattcaccnc accggaactn gtangatcca ctnnttctat
                                                                       660
aaccggncgc caccgcnnnt ggaactccac tettnttncc tttacttgag ggttaaggte
                                                                       720
accettnneg ttacettggt ccaaacentn centgtgteg anatngtnaa tenggneena
                                                                       780
tnccancene atangaagee ng
                                                                       802
      <210> 19
      <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (731)
      <223> n = A,T,C or G
      <400> 19
cnaagettee aggtnaeggg eegenaanee tgaeeenagg tancanaang eagnengegg
                                                                        60
gagcccaccg tcacgnggng gngtctttat nggagggggc ggagccacat cnctggacnt
                                                                       120
entgacecca acteceence nencantgea gtgatgagtg cagaactgaa eggtnacgtgg
                                                                       180
caggaaccaa gancaaanne tgeteennte caagteggen nagggggegg ggetggecae
                                                                       240
geneateent enagtgetgn aaageeeenn eetgtetaet tgtttggaga aengennnga
                                                                       300
```

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catgeccagn gttanataac nggengagag tnantttgec tetecettee qqetqeqean
                                                                       360
cgngtntgct tagnggacat aacctgacta cttaactgaa cccnngaatc tnccncccct
                                                                       420
ccactaaget cagaacaaaa aacttegaca ccacteantt gteacetgne tgeteaagta
                                                                       480
aagtgtaccc catneccaat gtntgetnga ngetetgnee tgenttangt teggteetgg
                                                                       540
gaagacctat caattnaagc tatgtttctg actgcctctt gctccctgna acaancnacc
                                                                       600
cnncnntcca aggggggnc ggccccaat cccccaacc ntnaattnan tttancccn
                                                                       660
ecceenggee eggeetttta enanentenn nnaengggna aaacennnge tttneccaae
                                                                       720
nnaatccncc t
                                                                       731
      <210> 20
      <211> 754
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(754)
      \langle 223 \rangle n = A,T,C or G
      <400> 20
ttttttttt tttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc
                                                                        60
caacccctc ntccaaatnn conttteegg gngggggtte caaacccaan ttanntttgg
                                                                       120
annttaaatt aaatnttnnt tggnggnnna anccnaatgt nangaaagtt naacccanta
                                                                       180
tnancttnaa tncctggaaa congtngntt ccaaaaatnt ttaaccctta anteceteg
                                                                       240
aaatngttna nggaaaaccc aanttctcnt aaggttgttt gaaggntnaa tnaaaanccc
                                                                       300
nnccaattgt ttttngccac gcctgaatta attggnttcc gntgttttcc nttaaaanaa
                                                                       360
ggnnancccc ggttantnaa tccccccnnc cccaattata ccganttttt ttngaattgg
                                                                       420
ganccenegg gaattaacgg ggnnnnteec tnttgggggg enggnneece eccenteggg
                                                                       480
ggttngggnc aggncnnaat tgtttaaggg tccgaaaaat ccctccnaga aaaaaanctc
                                                                       540
ccaggntgag nntngggttt ncccccccc canggcccct ctcgnanagt tggggtttgg
                                                                       600
ggggcctggg attttntttc ccctnttncc tcccccccc ccnggganag aggttngngt
                                                                       660
tttgntcnnc ggccccnccn aaganctttn ccganttnan ttaaatccnt gcctnggcga
                                                                       720
agtccnttgn agggntaaan ggccccctnn cggg
                                                                       754
      <210> 21
      <211> 755
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(755)
      <223> n = A,T,C or G
      <400> 21
atcancecat gacecenaac nngggaeene teanceggne nnnenacene eggeenatea
                                                                       60
nngtnagnnc actnennttn natcaenece encenactae gecenenane enaegeneta
                                                                      120
nncanatnce actganngeg egangtngan ngagaaanet nataccanag neaccanaen
                                                                      180
ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnancctc cnaagtattn
                                                                      240
nnenneanat gatttteetn anecgattae centneecce tanecectee eccecaaena
                                                                      300
cgaaggenet ggneenaagg nngegnenee cegetagnte ecenneaagt eneneneeta
                                                                      360
aactcancen nattacnege ttentgagta teactceecg aateteacee tactcaacte
                                                                      420
aaaaanatcn gatacaaaat aatncaagcc tgnttatnac actntqactq qqtctctatt
                                                                      480
ttagnggtcc ntnaanchtc ctaatacttc cagtctncct tcnccaattt ccnaanggct
                                                                      540
ctttcngaca gcatnttttg gttcccnntt gggttcttan ngaattgccc ttcntngaac
                                                                      600
```

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gggctcntct tttccttcgg ttancctggn ttcnnccggc cagttattat ttcccntttt
                                                                       660
aaattentne entttanttt tggenttena aacceegge ettgaaaaeg geeceetggt
                                                                       720
aaaaggttgt tttganaaaa tttttgtttt gttcc
                                                                       755
      <210> 22
      <211> 849
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(849)
      <223> n = A,T,C \text{ or } G
      <400> 22
tttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt
                                                                        60
acgctnggan taangcgacc cganttctag gannenccct aaaatcanac tgtgaagatn
                                                                       120
atcctgnnna cggaanggtc accggnngat nntgctaggg tgnccnctcc cannnenttn
                                                                       180
cataacteng nggccctgcc caccaccttc ggcggcccng ngnccgggcc cgggtcattn
                                                                       240
gnnttaacen caetnngena neggttteen neecenneng accenggega teeggggtne
                                                                       300
tctgtcttcc cctgnagncn anaaantggg ccncggnccc ctttacccct nnacaagcca
                                                                       360
engeenteta neenengeee eeeeteeant nngggggaet geenannget eegttnetng
                                                                       420
nnacccennn gggtneeteg gttgtegant enacegnang ceanggatte enaaggaagg
                                                                       480
tqcqttnttg gcccctaccc ttcgctncgg nncacccttc ccgacnanga nccgctcccg
                                                                       540
enennegning cetenecteg caacaceege netentengt negginnece ecceaceege
                                                                       600
necetenene ngnegnanen eteeneenee gteteannea eeaceegee eegecaggee
                                                                       660
ntcanceach ggnngachng nagchennte geneegegen gegneneet egeenengaa
                                                                       720
ctnentengg ccantinge teaaneenna chaaacgeeg etgegegee egnagegnee
                                                                       780
ncctccncga gtcctcccgn cttccnaccc angnnttccn cgaggacacn nnaccccgcc
                                                                       840
nncangcgg
                                                                       849
      <210> 23
      <211> 872
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(872)
      <223> n = A,T,C or G
      <400> 23
gegeaaacta tacttegete gnactegtge geetegetne tetttteete egeaaceatg
                                                                       60
totgacnano cogattnggo ngatatonan aagntogano agtocaaact gantaacaca
                                                                       120
cacachenan aganaaatee netgeettee anagtanaen attgaaenng agaaceange
                                                                      180
nggcgaatcg taatnaggcg tgcgccgcca atntgtcncc gtttattntn ccagcntcnc
                                                                      240
ctnccnaccc tacntetten nagetgtenn acccetngtn cgnaccccc naggtegga
                                                                      300
tegggtttnn nntgacegng enneceetee eccentecat nacganeene eegeaceaee
                                                                      360
nanngenege neecegnnet ettegeenee etgteetntn eecetginge etggenengn
                                                                      420
accgcattga ccctcgccnn ctncnngaaa ncgnanacgt ccgggttgnn annancgctg
                                                                      480
tgggnnngcg tetgeneege gtteetteen nennetteea ecatettent taengggtet
                                                                      540
concecent tennaceane cetaggacge threethige ecceptinae teccecett
                                                                      600
cgncgtgncc cgnccccacc ntcatttnca nacgntcttc acaannncct ggntnnctcc
                                                                      660
cnancngnen gteaneenag ggaagggngg ggnneenntg nttgaegttg nggngangte
                                                                      720
cgaanantcc tencentean enctaceeet egggegnnet etengttnee aaettaneaa
                                                                      780
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ntetecceg ngngemente teagestene concecenet etetgeantg thetetgete
                                                                       840
tnaccnntac gantnttcgn cnccctcttt cc
                                                                       872
      <210> 24
      <211> 815
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(815)
      <223> n = A,T,C or G
      <400> 24
gcatgcaagc ttgagtattc tatagngtca cctaaatanc ttggcntaat catggtcnta
                                                                       60
nctgncttcc tgtgtcaaat gtatacnaan tanatatgaa tctnatntga caaganngta
                                                                       120
tentneatta gtaacaantg tnntgteeat eetgtengan canatteeca tnnattnegn
                                                                      180
cgcattcncn geneantath taatngggaa ntennntnnn neacenneat etatentnee
                                                                      240
genecetgae tggnagagat ggatnantte tnntntgace nacatgttea tettggattn
                                                                      300
aanancecee egengneeae eggtingnng enageennie ecaagacete etgiggaggi
                                                                      360
aacctgcgtc aganncatca aacntgggaa accegcnncc angtnnaagt ngnnncanan
                                                                      420
gatecegtee aggnttnace atceettene agegeeecet tingtgeett anagngnage
                                                                      480
gtgtccnanc cnctcaacat ganacgcgcc agnccanccg caattnggca caatgtcqnc
                                                                      540
gaacccccta gggggantna thcaaanccc caggattgtc chchcangaa atcccncanc
                                                                      600
cccnccctac ccnnctttgg gacngtgacc aantcccgga gtnccagtcc ggccngnctc
                                                                      660
ccccaccggt nnccntgggg gggtgaanct cngnntcanc cngncgaggn ntcgnaagga
                                                                      720
accggncctn ggncgaanng ancnntcnga agngccncnt cgtataaccc cccctcncca
                                                                      780
nccnacngnt agntcccccc engggtnegg aangg
                                                                      815
      <210> 25
      <211> 775
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(775)
     <223> n = A,T,C or G
      <400> 25
ccgagatgtc tcgctccgtg gccttagctg tgctcgcgct actctctt tctggcctgq
                                                                       60
aggetateca gegtaeteca aagatteagg tttaeteaeg teateeagea gagaatggaa
                                                                      120
agtcaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt qaanttgact
                                                                      180
tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg
                                                                      240
actggtcttt ctatctcntg tactacactg aattcacccc cactgaaaaa gatgagtatg
                                                                      300
cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca
                                                                      360
tgtaagcagn cnncatggaa gtttgaagat gccgcatttg gattggatga attccaaatt
                                                                      420
ctgcttgctt gcnttttaat antgatatgc ntatacaccc taccctttat gnccccaaat
                                                                      480
tgtaggggtt acatnantgt tenentngga catgatette etttataant cencentteg
                                                                      540
aattgcccgt cncccngttn ngaatgtttc cnnaaccacg gttggctccc ccaggtcncc
                                                                      600
tettaeggaa gggeetggge enetttneaa ggttggggga acenaaaatt tenettntge
                                                                      660
conceencea ennicitigng nnencantit ggaaccette enaiteceet tggeetenna
                                                                      720
nccttnncta anaaaacttn aaancgtngc naaanntttn acttcccccc ttacc
                                                                      775
```

```
<211> 820
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(820)
       <223> n = A,T,C or G
       <400> 26
 anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat
                                                                         60
 cccanagata ncttatanca acagtgcttt gaccaagagc tgctgggcac atttcctgca
                                                                        120
gaaaaggtgg cggtccccat cactcctcct ctcccatagc catcccagag gggtgagtag
                                                                        180
 ccatcangcc ttcggtggga gggagtcang gaaacaacan accacagagc anacagacca
                                                                        240
ntgatgacca tgggcgggag cgagcctctt ccctgnaccg gggtggcana nganaqccta
                                                                        300
nctgaggggt cacactataa acgttaacga ccnagatnan cacctgcttc aagtgcaccc
                                                                        360
 tteetacetg acnaceagng accnnnaact gengeetggg gacagenetg gganeageta
                                                                        420
 acnnageact cacetgeece eccatggeeg thegenteec tggteetgne aagggaaget
                                                                        480
ccctgttgga attncgggga naccaaggga nccccctcct ccanctgtga aggaaaaann
                                                                        540
gatggaattt thecetteeg geennteece tetteettta caegeeecet nntactente
                                                                        600
tecetetntt nteetgnene aettttnace cennnattte eettnattga teggannetn
                                                                        660
ganattccac tnncgcctnc cntcnatcng naanacnaaa nactntctna cccnggggat
                                                                        720
gggnncctcg ntcatcctct ctttttcnct accnccnntt ctttgcctct ccttnqatca
780tccaacente gntggeentn cececeennn teetttneee
820
       <210> 27
       <211> 818
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(818)
       <223> n = A,T,C or G
       <400> 27
 tctgggtgat ggcctcttcc tcctcaggga cctctgactg ctctgggcca aagaatctct
                                                                        60
 tgtttcttct ccgagcccca ggcagcggtg attcagccct gcccaacctg attctgatqa
                                                                        120
ctgcggatgc tgtgacggac ccaaggggca aatagggtcc cagggtccag ggaggggcgc
                                                                        180
ctgctgagca cttccgcccc tcaccctgcc cagcccctgc catgagctct qqqctqqqtc
                                                                       240
tecgeeteca gggttetget ettecangea ngecancaag tggegetggg ceacactgge
                                                                       300
 ttetteetge ecenteeetg getetgante tetgtettee tgteetgtge angeneettg
                                                                       360
gatctcagtt tecetenete anngaactet gtttetgann tetteantta actntqantt
                                                                       420
tatnaccnan tggnctgtnc tgtcnnactt taatgggccn gaccggctaa tccctccctc
                                                                       480
netecettee anttennnna accngettne ententetee centaneceg cengggaane
                                                                       540
ctcctttgcc ctnaccangg gccnnnaccg cccntnnctn ggggggenng gtnnctncnc
                                                                       600
etgntnncce enetenennt theetegtee ennennegen nngeanntte nengteeenn
                                                                       660
 tnnctctten ngtntegnaa ngntenentn tnnnnngnen ngntnntnen teeetetene
                                                                       720
cnnntgnang tnnttnnnnc ncngnncccc nnnncnnnnn nggnnntnnn tctncncngc
                                                                       780
cccnncccc ngnattaagg cctccnntct ccggccnc
                                                                       818
       <210> 28
       <211> 731
       <212> DNA
```

```
<213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(731)
      <223> n = A,T,C or G
      <400> 28
aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtqtq
                                                                        60
tcccaacatg anggtgnngt tctcttttga angagggttg ngtttttann ccnggtgggt
                                                                       120
gattnaaccc cattgtatgg agnnaaaggn tttnagggat ttttcggctc ttatcaqtat
                                                                       180
ntanatteet gtnaategga aaatnatntt tennenggaa aatnttgete ceateegnaa
                                                                       240
attnetcccg ggtagtgcat nttngggggn cngccangtt tcccaggctq ctanaatcqt
                                                                       300
actaaagntt naagtgggan tncaaatgaa aacctnncac agagnatccn tacccgactg
                                                                       360
tnnnttncct tcgccctntg actctgcnng agcccaatac ccnngngnat gtcncccngn
                                                                       420
nnnqcgncnc tgaaannnnc tcgnggctnn gancatcang gggtttcgca tcaaaagcnn
                                                                       480
egitteneat naaggeacti ingecteate caaceneing ecetenneca titingeegie
                                                                       540
nggttenect aegetnntng encetnnntn ganattttne eegeetnggg naanceteet
                                                                       600
gnaatgggta gggncttntc ttttnaccnn gnggtntact aatcnnctnc acgcntnctt
                                                                       660
tetenacee eccettitt caateecane ggenaatggg gteteceenn eqanqqqqq
                                                                       720
nnncccannc c
                                                                       731
      <210> 29
      <211> 822
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(822)
      <223> n = A,T,C or G
actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttaqat
                                                                        60
egeteanace teacancete cenaenange etataangaa nannaataga netgtnennt
                                                                       120
aththtache teatanneet ennnaceeae teeetettaa eeentaetgt geetatngen
                                                                       180
thnctantct ntgccgcctn chanceacch gtgggccnac chennghatt ctcnatctcc
                                                                       240
tenecatnin gectananta ngineatace etatacetae necaatgeta nnnetaanen
                                                                      300
tocatnantt annntaacta ccactgacht ngactttone athanetect aatttgaate
                                                                      360
tactctgact cccacngcct annnattagc anchtccccc nachathtct caaccaaatc
                                                                      420
ntcaacaacc tatctanctg ttcnccaacc nttncctccg atccccnnac aacccccctc
                                                                      480
ccaaataccc nccacctgac ncctaacccn caccatcccg gcaagccnan ggncatttan
                                                                      540
ccactggaat cacnatngga naaaaaaaac ccnaactctc tancncnnat ctccctaana
                                                                      600
aatnotootn naatttactn noantnocat caanoccacn tgaaacnnaa cocctgtttt
                                                                      660
tanatecett etttegaaaa eenaceettt annneecaae ettingggee eeeeeneine
                                                                      720
ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg
                                                                      780
canatectat ceettanttn ggggneeett neeengggee ee
                                                                      822
      <210> 30
      <211> 787
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
```

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<222> (1)...(787)
      <223> n = A, T, C or G
      <400> 30
eggeegeetg etetggeaca tgeeteetga atggeateaa aagtgatgga etgeecattg
                                                                        60
ctagagaaga ccttctctcc tactgtcatt atggagccct gcagactgag ggctcccctt
                                                                       120
gtotgcagga titgatgtot gaagtogtgg agtgtggctt ggagotocto atotacatna
                                                                       180
getggaagee etggagggee tetetegeea geeteeeet teteteeaeg etetecangg
                                                                       240
acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga
                                                                       300
cccatggggc ctgnaaggcc agggtctcct ttgacaccat ctctcccgtc ctgcctqqca
                                                                       360
ggccgtggga tccactantt ctanaacggn cgccaccncg gtgggagctc cagcttttgt
                                                                       420
tecenttaat gaaggttaat tgenegettg gegtaateat nggteanaac tnttteetgt
                                                                       480
gtgaaattgt ttntcccctc ncnattccnc ncnacatacn aacccqqaan cataaaqtgt
                                                                       540
taaagcctgg gggtngcctn nngaatnaac tnaactcaat taattgcgtt ggctcatggc
                                                                       600
ccgctttccn ttcnggaaaa ctgtcntccc ctgcnttnnt gaatcggcca cccccnggg
                                                                       660
aaaagcggtt tgcnttttng ggggntcctt conctteece cetenetaan ceetnegeet
                                                                       720
cggtcgttnc nggtngcggg gaangggnat nnnctcccnc naagggggng agnnngntat
                                                                       780
ccccaaa
                                                                       787
      <210> 31
      <211> 799
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) . . . (799)
      <223> n = A,T,C or G
      <400> 31
ttttttttt ttttttggc gatgctactg tttaattgca ggaggtgggg gtgtgtgtac
                                                                        60
catgtaccag ggctattaga agcaagaagg aaggagggag ggcagagcgc cctgctgagc
                                                                       120
aacaaaggac teetgeagee ttetetgtet gtetettgge geaggeacat ggggaggeet
                                                                       180
cccgcagggt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg
                                                                       240
gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca
                                                                       300
ggggaccttc tgttctccca nggnaacttc ntnnatctcn aaaqaacaca actqtttctt
                                                                       360
engeanttet ggetgtteat ggaaageaca ggtgteenat ttnggetggg acttggtaca
                                                                       420
tatggttccg gcccacctct cccntcnaan aagtaattca ccccccccn ccntctnttq
                                                                       480
cctgggccct taantaccca caccggaact canttantta ttcatcttng gntgggcttg
                                                                      540
ntnatchech eetgaangeg eeaagttgaa aggeeaegee gtheeenete eecatagnan
                                                                      600
nttttnncnt canctaatge ecceeengge aacnateeaa teeeeceen tgggggeece
                                                                      660
ageceangge eccegneteg ggnnneengn enegnantee ecaggntete ceantengne
                                                                      720
connigence ecceptagea gaacanaagg ningageene egeanninnin ngqtinenae
                                                                      780
ctcgccccc cennegnng
                                                                      799
      <210> 32
      <211> 789
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(789)
      <223> n = A,T,C or G
```

```
<400> 32
60
ttttnccnag ggcaggttta ttgacaacct cncgggacac aancaggctg gggacaggac
                                                                     120
ggcaacaggc tccggcggcg gcggcggcgg ccctacctgc ggtaccaaat ntqcaqcctc
                                                                     180
cgctcccgct tgatnttcct ctgcagctgc aggatgccnt aaaacagggc ctcggccntn
                                                                     240
ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcqcancc cctcaccacc
                                                                     300
nattaggaat agtggtntta cocncenceg ttggcncact cocentggaa accaettnte
                                                                     360
geggeteegg catetggtet taaacettge aaacnetggg gecetetttt tggttantnt
                                                                     420
neengecaca atcatnacte agactggene gggetggece caaaaaanen eeccaaaace
                                                                     480
ggnccatgtc ttnncggggt tgctgcnatn tncatcacct cccgggcnca ncaggncaac
                                                                     540
ccaaaagttc ttgnggcccn caaaaaanct ccggggggnc ccagtttcaa caaagtcatc
                                                                     600
ccccttggcc cccaaatcct cccccgntt nctgggtttq qqaacccacq cctctnnctt
                                                                     660
tggnnggcaa gntggntccc ccttcgggcc cccggtgggc ccnnctctaa ngaaaacncc
                                                                     720
ntectnnnea ceateceece nngnnaegne tancaangna teeettttt tanaaaeggg
                                                                     780
cccccncq
                                                                     789
      <210> 33
      <211> 793
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(793)
      <223> n = A,T,C or G
      <400> 33
gacagaacat gttggatggt ggagcacctt tctatacgac ttacaggaca gcagatgggg
                                                                      60
aattcatggc tgttggagca atanaacccc agttctacga gctgctgatc aaaggacttg
                                                                     120
gactaaagtc tgatgaactt cccaatcaga tgagcatgga tgattggcca gaaatgaana
                                                                     180
agaagtttgc agatgtattt gcaaagaaga cgaaggcaga gtggtgtcaa atctttgacg
                                                                     240
gcacagatgc ctgtgtgact ccggttctga cttttgagga ggttgttcat catgatcaca
                                                                     300
acaangaacg gggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac
                                                                     360
ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc
                                                                     420
ggncgccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct
                                                                     480
tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac
                                                                     540
acaacatacg anceggaage atnaaatttt aaageetggn ggtngeetaa tgantgaact
                                                                     600
nactcacatt aattggcttt gcgctcactg cccgctttcc agtccggaaa acctgtcctt
                                                                     660
gccagctgcc nttaatgaat cnggccaccc cccggggaaa aggcngtttg cttnttqqqq
                                                                     720
egenetteec getttetege tteetgaant cetteeceec ggtetttegg ettgeggena
                                                                     780
acggtatcna cct
                                                                     793
      <210> 34
      <211> 756
      <212> DNA
     <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(756)
      <223> n = A,T,C or G
      <400> 34
gccgcgaccg gcatgtacga gcaactcaag ggcgagtgga accgtaaaag ccccaatctt
                                                                     60
ancaagtgcg gggaanagct gggtcgactc aagctagttc ttctggagct caacttcttg
                                                                    120
```

```
ccaaccacag ggaccaagct gaccaaacag cagctaattc tggcccgtga catactggaq
                                                                       180
atcggggccc aatggagcat cctacgcaan gacatcccct ccttcgagcg ctacatggcc
                                                                       240
cageteaaat getaetaett tgattaeaan gageagetee eegagteage etatatgeae
                                                                       300
cagetettgg gceteaacet cetetteetg etgteecaga acegggtgge tgantnecae
                                                                       360
acgganttgg ancggctgcc tgcccaanga catacanacc aatgtctaca tcnaccacca
                                                                       420
gtgtcctgga gcaatactga tgganggcag ctaccncaaa gtnttcctgg ccnaqqqtaa
                                                                       480
catececege egagagetae acettettea tigacateet getegacaet atcagggatg
                                                                       540
aaaatcgcng ggttgctcca gaaaggctnc aanaanatcc ttttcnctga aggccccgg
                                                                       600
atnonctagt notagaatcg goodgocatc goggtgganc otocaacctt togttnooct
                                                                       660
ttactgaggg ttnattgccg cccttggcgt tatcatggtc acnccngttn cctgtgttga
                                                                       720
aattnttaac ccccacaat tccacgccna cattng
                                                                       756
      <210> 35
      <211> 834
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(834)
      <223> n = A,T,C or G
      <400> 35
ggggatctet anatchacct gnatgcatgg ttgtcggtgt ggtcgctgtc gatgaanatg
                                                                        60
aacaggatet tgeeettgaa getetegget getgtnttta agttgeteag tetgeegtea
                                                                       120
tagtcagaca cnctcttggg caaaaaacan caggatntga gtcttgattt cacctccaat
                                                                       180
aatcttengg getgtetget eggtgaacte gatgaenang ggeagetggt tgtgtntgat
                                                                       240
aaantccanc angtteteet tggtgacete ceetteaaag ttgtteegge etteateaaa
                                                                       300
cttctnnaan angannance canctttgtc gagetggnat ttgganaaca cqtcactqtt
                                                                       360
ggaaactgat cccaaatggt atgtcatcca tcgcctctgc tgcctgcaaa aaacttgctt
                                                                       420
ggcncaaatc cgactccccn tccttgaaag aagccnatca caccccctc cctggactcc
                                                                       480
nncaangact ctnccgctnc cccntccnng cagggttggt ggcannccgg gcccntgcgc
                                                                       540
ttetteagee agtteaenat ntteateage ecetetgeea getgttntat teettqqqqq
                                                                       600
ggaancegte tetecettee tgaannaact ttgacegtng gaatageege gentencent
                                                                       660
acninctggg ccgggttcaa antccctccn ttgncnntcn cctcgggcca ttctggattt
                                                                       720
nccnaacttt ttccttcccc cnccccncgg ngtttggntt tttcatnggg ccccaactct
                                                                       780
getnttggcc antecectgg gggentntan encecetnt ggtecentng ggec
                                                                       834
      <210> 36
      <211> 814
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(814)
      <223> n = A,T,C or G
      <400> 36
eggnegettt cengeegege eeegttteea tgacnaagge teeetteang ttaaataenn
                                                                        60
cctagnaaac attaatgggt tgctctacta atacatcata cnaaccagta aqcctqccca
                                                                       120
naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggtctctcc accccctgta
                                                                       180
ggaaaggcct gccttgtaag acaccacaat ncggctgaat ctnaaqtctt qtqttttact
                                                                      240
aatggaaaaa aaaaataaac aanaggtttt gttctcatgg ctgcccaccg caqcctqqca
                                                                      300
ctaaaacanc ccagegetea ettetgettg ganaaatatt etttgetett ttggacatea
                                                                      360
```

```
ggcttgatgg tatcactgcc acntttccac ccagctgggc ncccttcccc catntttqtc
                                                                       420
antganctgg aaggeetgaa nettagtete caaaagtete ngeecacaag aceggeeace
                                                                       480
aggggangtc ntttncagtg gatctgccaa anantacccn tatcatcnnt gaataaaaag
                                                                       540
gccctgaac ganatgcttc cancancctt taagacccat aatcctngaa ccatggtgcc
                                                                       600
cttccggtct gatccnaaag gaatgttcct gggtcccant ccctcctttq ttncttacqt
                                                                       660
tgtnttggac centgetngn atnacecaan tganatecee ngaageacee tneecetgge
                                                                       720
atttganttt cntaaattct ctgccctacn nctgaaagca cnattccctn qqcnccnaan
                                                                       780
ggngaactca agaaggtctn ngaaaaacca cncn
                                                                       814
      <210> 37
      <211> 760
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(760)
      <223> n = A,T,C or G
      <400> 37
geatgetget etteeteaaa gttgttettg ttgccataac aaccaccata ggtaaagegg
                                                                        60
gcgcagtgtt cgctgaaggg gttgtagtac cagcgcggga tgctctcctt gcagagtcct
                                                                       120
gtgtctggca ggtccacgca atgccctttg tcactgggga aatggatgcg ctggagctcg
                                                                       180
tenaaneeae tegtgtattt tteacangea geeteeteeg aagenteegg geagttqqqq
                                                                       240
gtgtcgtcac actccactaa actgtcgatn cancagccca ttgctgcagc qqaactqqqt
                                                                       300
gggctgacag gtgccagaac acactggatn ggcctttcca tggaagggcc tgggggaaat
                                                                       360
cncctnance caaactgeet etcaaaggee acettgeaca eecegacagg etagaaatge
                                                                       420
actictictic ccaaaggtag tigtictigt tgcccaagca ncctccanca aaccaaaanc
                                                                       480
ttgcaaaatc tgctccgtgg gggtcatnnn taccanggtt ggggaaanaa acccqqcnqn
                                                                      540
gancencett gtttgaatge naaggnaata atecteetgt ettgettggg tggaanagea
                                                                      600
caattgaact gttaacnttg ggccgngttc cnctngggtg gtctgaaact aatcaccgtc
                                                                      660
actggaaaaa ggtangtgcc ttccttgaat tcccaaantt cccctnqntt tqqqtnnttt
                                                                      720
ctcctctncc ctaaaaatcg tnttcccccc ccntanggcg
                                                                      760
      <210> 38
      <211> 724
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(724)
      <223> n = A,T,C or G
      <400> 38
ttttttttt tttttttt tttttttt tttttaaaaa cccctccat tqaatqaaaa
                                                                       60
cttccnaaat tgtccaaccc cctcnnccaa atnnccattt ccggggggg gttccaaacc
                                                                      120
caaattaatt ttgganttta aattaaatnt tnattngggg aanaanccaa atgtnaagaa
                                                                      180
aatttaaccc attatnaact taaatnootn gaaacccntg gnttocaaaa atttttaacc
                                                                      240
cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaaggtt
                                                                      300
ngatttaaac ccccttnant tnttttnacc cnngnctnaa ntatttngnt tccqqtqttt
                                                                      360
tectnttaan entnggtaac teeegntaat gaannneet aanceaatta aacegaattt
                                                                      420
tttttgaatt ggaaattccn ngggaattna ccggggtttt tcccntttqq qqqccatncc
                                                                      480
cccnctttcg gggtttgggn ntaggttgaa tttttnnang ncccaaaaaa ncccccaana
                                                                      540
aaaaaactcc caagnnttaa ttngaatntc ccccttccca ggccttttgg gaaaggnggg
                                                                      600
```

```
tttntggggg congggantt cnttcccccn ttnccnccc cccccnggt aaangqttat
                                                                       660
ngnntttggt ttttgggccc cttnanggac cttccqqatn qaaattaaat ccccqqqncq
                                                                       720
gccg
                                                                       724
      <210> 39
      <211> 751
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(751)
      \langle 223 \rangle n = A,T,C or G
      <400> 39
tttttttttt tttttctttg ctcacattta atttttattt tgatttttt taatgctgca
                                                                        60
caacacaata tttatttcat ttgtttcttt tatttcattt tatttgtttg ctgctqctqt
                                                                       120
tttatttatt tttactgaaa gtgagaggga acttttgtgg ccttttttcc ttttcctqta
                                                                       180
ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aaggqqqttt
                                                                       240
cgcaaaatca ctcgggggaa nggaaaggtt gctttgttaa tcatgcccta tqqtqqqtqa
                                                                       300
ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc tttaattana
                                                                       360
cttgggggtt ccctccccan accaaccccn ctgacaaaaa gtgccngccc tcaaatnatg
                                                                       420
teceggennt enttgaaaca caengengaa ngtteteatt nteecenene cagginaaaa
                                                                       480
tgaagggtta ccatntttaa cnccacctcc acntggcnnn gcctgaatcc tcnaaaancn
                                                                       540
ccctcaancn aattnetnng ccccggtene gentnngtee eneceggget ccgggaantn
                                                                       600
caccccnga annenntnne naacnaaatt cegaaaatat teeenntene teaatteeee
                                                                       660
cnnagactnt cctcnncnan cncaattttc ttttnntcac gaacncgnnc cnnaaaatgn
                                                                       720
nnnncncctc cnctngtccn naatcnccan c
                                                                       751
     <210> 40
     <211> 753
      <212> DNA
    <213> Homo sapien
     <220>
     <221> misc_feature
      <222> (1)...(753)
     <223> n = A,T,C or G
      <400> 40
gtggtatttt ctgtaagatc aggtgttcct ccctcgtagg tttagaggaa acaccctcat
                                                                        60
agatgaaaac cccccgaga cagcagcact gcaactgcca agcagccggg gtaggagggg
                                                                       120
egecetatge acagetggge cettgagaca geagggette gatgteagge tegatgteaa
                                                                       180
tggtctggaa gcggcggctg tacctgcgta ggggcacacc gtcagggccc accaggaact
                                                                       240
tctcaaagtt ccaggcaacn tcgttgcgac acaccggaga ccaggtgatn agcttggggt
                                                                       300
cggtcataan cgcggtggcg tcgtcgctgg gagctggcag ggcctcccgc agqaaqqcna
                                                                       360
ataaaaggtg cgccccgca ccgttcanct cgcacttctc naanaccatg angttgggct
                                                                       420
cnaacccacc accanneegg actteettga nggaatteec aaatetette gntettggge
                                                                       480
ttctnctgat gccctanctg gttgcccngn atgccaanca nccccaancc ccqqqqtcct
                                                                       540
aaancaccon cotcotontt toatotgggt tnttntcccc ggacontggt toctotcaaq
                                                                       600
ggancccata tetenacean tacteacent necececent gnnacccane ettetanngn
                                                                       660
ttcccncccg ncctctggcc cntcaaanan gcttncacna cctgggtctg ccttccccc
                                                                       720
tnccctatct gnaccccncn tttgtctcan tnt
                                                                       753
```

```
<211> 341
      <212> DNA
      <213> Homo sapien
      <400> 41
actatatcca tcacaacaga catgcttcat cccatagact tcttgacata gcttcaaatg
                                                                        60
agtgaaccca tccttgattt atatacatat atgttctcag tattttggga gcctttccac
                                                                        120
ttctttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt
                                                                       180
tatagcttgt ttacgtagta agtttttgaa gtctacattc aatccagaca cttagttgag
                                                                       240
tgttaaactg tgatttttaa aaaatatcat ttgagaatat tctttcagag gtattttcat
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ttttactttt tgattaattg tgttttatat attagggtag t
                                                                       341
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      <211> 101
      <212> DNA
      <213> Homo sapien
      <400> 42
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gtttcaaaca ttctaaataa ataattttca gtggcttcat a
                                                                       101
      <210> 43
      <211> 305
      <212> DNA
      <213> Homo sapien
      <400> 43
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tccagggtgg tctcacactg taattagagc tattgaggag tctttacagc aaattaagat
                                                                       120
tragatgeet tgetaagtet agagttetag agttatgttt cagaaagtet aagaaaccea
                                                                       180
cctcttgaga ggtcagtaaa gaggacttaa tatttcatat ctacaaaatg accacaggat
                                                                       240
tggatacaga acgagagtta tcctggataa ctcagagctg agtacctgcc cgggggccgc
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tcgaa
                                                                       305
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      <211> 852
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(852)
      <223> n = A,T,C or G
      <400> 44
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                                                                        60
gattatttgg tgtgtgtttt ggtttgtgtc caaagtattg gcagcttcag ttttcatttt
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ctctccatcc tcgggcattc ttcccaaatt tatataccag tcttcgtcca tccacacgct
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ccagaatttc tcttttgtag taatatctca tagctcggct gagcttttca taggtcatgc
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tgctgttgtt cttcttttta ccccataget gagccactgc ctctgatttc aagaacctga
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agacgccctc agatcggtct tcccatttta ttaatcctgg gttcttgtct gggttcaaqa
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ggatgtcgcg gatgaattcc cataagtgag tccctctcgg gttgtgcttt ttggtgtggc
                                                                       420
acttggcagg ggggtcttgc tcctttttca tatcaggtga ctctgcaaca ggaaggtgac
                                                                       480
tggtggttgt catggagatc tgagcccggc agaaagtttt gctgtccaac aaatctactg
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tgctaccata gttggtgtca tataaatagt tctngtcttt ccaggtgttc atgatggaag
                                                                       600
```

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gctcagtttg ttcagtcttg acaatgacat tgtgtgtgga ctggaacagg tcactactgc
                                                                        660
actggccgtt ccacttcaga tgctgcaagt tgctgtagag gagntgcccc gccgtccctg
                                                                        720
ccgcccgggt gaactcctgc aaactcatgc tgcaaaggtg ctcgccgttg atgtcgaact
                                                                        780
cntggaaagg gatacaattg gcatccagct ggttggtgtc caggaggtga tggagccact
                                                                        840
cccacacctg gt
                                                                        852
      <210> 45
      <211> 234
      <212> DNA
      <213> Homo sapien
      <400> 45
acaacagacc cttgctcgct aacgacctca tgctcatcaa gttggacgaa tccgtgtccg
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agtotgacac catcoggage atcagcattg ottogcagtg coctacogcg gggaactott
                                                                       120
gcctcgtttc tggctggggt ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg
                                                                       180
tgaacgtgtc ggtggtgtct gaggaggtct gcagtaagct ctatgacccq ctgt
                                                                       234
      <210> 46
      <211> 590
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(590)
      <223> n = A,T,C or G
      <400> 46
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atttgatagc aatattttgg agattacaga gttttagtaa ttaccaatta cacagttaaa
                                                                       120
aagaagataa tatattccaa gcanatacaa aatatctaat gaaagatcaa ggcaggaaaa
                                                                       180
tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta
                                                                       240
aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat
                                                                       300
caggataaan aactgaaggg canaaagaat taattttcac ttcatgtaac ncacccanat
                                                                       360
ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc
                                                                       420
tggtctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag
                                                                       480
ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct
                                                                       540
gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt
                                                                       590
      <210> 47
      <211> 774
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(774)
      <223> n = A,T,C \text{ or } G
      <400> 47
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                                                                        60
tgaacagaat tttcctgnac aacggggctt caaaataatt ttcttgggga ggttcaagac
                                                                       120
gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg
                                                                       180
cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa
                                                                       240
aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggctct
                                                                       300
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cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctcctgtgtg
                                                                        360
ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc
                                                                        420
ccacactect tgaacacaca tececaggtt atatteetgg acatggetga acetectatt
                                                                        480
cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccactcac cctccaaacc
                                                                        540
acggcatggg aagcctttct gacttgcctg attactccag catcttggaa caatccctga
                                                                        600
ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttggagcc
                                                                        660
aggetgetgg cttcaaattn tggeteattt acgagetatg ggacettggg caagtnatet
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tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt
                                                                        774
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      <211> 124
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(124)
      <223> n = A,T,C or G
      <400> 48
canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt
                                                                        60
ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact
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tggt
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      <210> 49
      <211> 147
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      \langle 223 \rangle n = A,T,C or G
      <400> 49
gccgatgcta ctattttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt
                                                                        60
tgtggctaca ggtggtgtct gactgcatna aaaanttttt tacgggtgat tgcaaaaaatt
                                                                       120
ttagggcacc catatcccaa gcantqt
                                                                       147
      <210> 50
      <211> 107
      <212> DNA
      <213> Homo sapien
      <400> 50
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                                                                        60
atggtttgag gttaggagga gttaggcata tgttttggga gaggggt
                                                                       107
      <210> 51
      <211> 204
      <212> DNA
      <213> Homo sapien
      <400> 51
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                                                                        60
```

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cgggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag
                                                                        120
gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttggcca
                                                                        180
cctccctttt gggaccagca atgt
                                                                        204
      <210> 52
      <211> 491
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(491)
      <223> n = A,T,C or G
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                                                                        60
gggtattttc caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca
                                                                       120
ccatcagaca ggtttttaaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa
                                                                       180
aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt
                                                                       240
tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtncc ctcaqtccca
                                                                       300
atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc
                                                                       360
atgcaacagt gtctttctt tncttttct ttttttttt ttacaggcac agaaactcat
                                                                       420
caattttatt tggataacaa agggtctcca aattatattg aaaaataaat ccaagttaat
                                                                       480
atcactcttg t
                                                                       491
      <210> 53
      <211> 484
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(484)
      <223> n = A, T, C or G
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gtattaacag tigcigaagi tiggiattit tatgcagcai titcittig cittgataac
                                                                       120
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct
                                                                       180
caatcaaatc tctacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct
                                                                       240
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc
                                                                       300
agetttgant ttetttgtge tgatangagg aaaggetgaa ttacettgtt geeteteeet
                                                                       360
aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncg
                                                                       420
tancttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc
                                                                       480
cant
                                                                       484
      <210> 54
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 54
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                                                                        60
ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag
                                                                       120
totatgtcct ctcaagtgcc tttttgtttg t
                                                                       151
```

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<210> 55
      <211> 91
      <212> DNA
      <213> Homo sapien
      <400> 55
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                                                                         60
gccctccagt ggatactcga gccaaagtgg t
                                                                         91
      <210> 56
      <211> 133
      <212> DNA
      <213> Homo sapien
      <400> 56
ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggact tgagtatact
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tggatttttg gtatctgtgg gttgggggga cggtccagga accaataccc catggatacc
                                                                       120
aagggacaac tgt
                                                                       133
      <210> 57
      <211> 147
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(147)
      <223> n = A,T,C or G
      <400> 57
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                                                                       60
gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana
                                                                       120
tctcantggg ctggatncat gcagggt
                                                                       147
      <210> 58
      <211> 198
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc_feature
      <222> (1)...(198)
      \langle 223 \rangle n = A,T,C or G
      <400> 58
acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc
                                                                        60
tgattacata catttatcct ttaaaaaaaga tgtaaatctt aatttttatg ccatctatta
                                                                       120
atttaccaat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt
                                                                       180
ttgacttcta agtttggt
                                                                       198
     <210> 59
     <211> 330
     <212> DNA
     <213> Homo sapien
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<400> 59					
acaacaaatg ggttgtgagg aa ccattgaaaa ttatcattaa tgcacctgtgct agcttgctaa aa tacagtcaat aaatgacaaa ggcagaaggaat ctatttatc actttcgtcttt attggacttc tt	gattttaaa tga atgggagtt aad ccagggcct aca catggatct cc	acaagtta ctctagag aggtggtt	tcaaaaactc caaatatagt tccagacttt	actcaatttt atcttctgaa ccagacccag taatgatatt	60 120 180 240 300 330
<210> 60 <211> 175 <212> DNA <213> Homo sapien					
<400> 60 accgtgggtg cettetacat to gtegtggget cetteetett ca teetggaace ageggtgget ge	atcctcatc cag	gctggtgc i	tgctcatcga	ctttgcgcac	60 120 175
<210> 61 <211> 154 <212> DNA <213> Homo sapien					
<400> 61 accccacttt tcctcctgtg ag ggttgttgct cttcaacagt at tggactgcac agccccgggg ct	cctcccct ttc	ccggatct g	gctacatgat gctgageegg	acagcagtgc :	60 120 154
<210> 62 <211> 30 <212> DNA <213> Homo sapien					
<400> 62 cgctcgagcc ctatagtgag tc	gtattaga				30
<210> 63 <211> 89 <212> DNA <213> Homo sapien					
<400> 63 acaagtcatt tcagcaccct tt ctgtatgaat aaaaatggtt at	gctcttca aaa gtcaagt	ictgacca t	cttttatat (	ttaatgette	60 89
<210> 64 <211> 97 <212> DNA <213> Homo sapien					
<400> 64 accggagtaa ctgagtcggg ac aatcagtgca tccaggattg gt	gctgaatc tga ccttggat ctg	atccacc a	ataaataaa q	ggttetgeag	60 97

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```
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      <211> 377
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      \langle 223 \rangle n = A,T,C or G
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gcatggcgtc ctaggccttg acacagcggc tggggtttgg gctntcccaa accgcacacc
                                                                        120
ccaaccctgg tctacccaca nttctggcta tgggctgtct ctgccactga acatcagggt
                                                                        180
tcggtcataa natgaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa
                                                                        240
ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaacccg
                                                                        300
tgggggtgaa ctacccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag
                                                                        360
gggcgggagg agcatgt
                                                                        377
      <210> 66
      <211> 305
      <212> DNA
      <213> Homo sapien
      <400> 66
acgeetttee etcagaatte agggaagaga etgtegeetg eetteeteeg ttgttgegtg
                                                                        60
agaacccgtg tgccccttcc caccatatcc accctcgctc catctttgaa ctcaaacacg
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aggaactaac tgcaccctgg tcctctcccc agtccccagt tcaccctcca tccctcacct
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tectecacte taagggatat caacactgee cageacaggg geeetgaatt tatgtggttt
                                                                       240
ttatatattt tttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac
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tgttt
                                                                       305
      <210> 67
      <211> 385
      <212> DNA
      <213> Homo sapien
      <400> 67
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ggtcggacca gccacatctc atgtgcaaga ttgcccagca gacatcaggt ctgagagttc
                                                                       120
cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc
                                                                       180
tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg
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ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg
                                                                       300
cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac
                                                                       360
catagittci gigciagigg accgi
                                                                       385
      <210> 68
      <211> 73
      <212> DNA
      <213> Homo sapien
      <400> 68
acttaaccag atatatttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa
                                                                        60
gtttttttaa tgg
                                                                        73
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<210> 69
      <211> 536
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(536)
      <223> n = A,T,C or G
      <400> 69
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                                                                        60
tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct
                                                                       120
cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat
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cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt
                                                                       240
cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt
                                                                       300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg
                                                                       360
ccgaaccata tgtaccaagt cccagcccaa cttggacacc tgtgccttcc atgaacagcc
                                                                       420
agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca
                                                                       480
gaangtccct gggtgaaatc caggtgtcaa gaaatcctan ggatctgttg ccaggc
                                                                       536
      <210> 70
      <211> 477
      <212> DNA
      <213> Homo sapien
     <400> 70
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                                                                        60
tcacttccac tccataacgc tcctcatact aggcctacta accaacacac taaccatata
                                                                       120
ccaatgatgg cgcgatgtaa cacgagaaag cacataccaa ggccaccaca caccacctgt
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ccaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc
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agggattttt ctgagccttt taccactcca gcctagcccc taccccccaa ctaggagggc
                                                                       300
actggccccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat
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ccgtattact cgcatcagga gtatcaatca cctgagctca ccatagtcta atagaaaaca
                                                                       420
açogaaacca aattattcaa agcactgott attacaattt tactgggtot ctatttt
                                                                       477
      <210> 71
      <211> 533
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(533)
      <223> n = A,T,C or G
      <400> 71
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                                                                        60
aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta
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tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat
                                                                       180
attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa qcatctcatt
                                                                       240
taaataaagg tttgtcatct ttaaaaaatac agcaatatgt gactttttaa aaaagctgtc
                                                                      300
aaataggtgt gaccctacta ataattatta gaaatacatt taaaaaacatc gagtacctca
                                                                      360
agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg
                                                                       420
cttcgtaatt ttggagtang aggttccctc ctcaattttg tatttttaaa aagtacatqq
                                                                      480
taaaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc
                                                                      533
```

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<210> 72
      <211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(511)
      <223> n = A,T,C or G
      <400> 72
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                                                                      60
aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa
                                                                     120
aageegeagg atgtetacae tataneagge getatttggg ttggetggag gagetgtgga
                                                                     180
aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt
                                                                     240
gaggttetet gtgtgeecac tggtttgaaa accgttetne aataatgata gaatagtaca
                                                                     300
cacatgagaa ctgaaatggc ccaaacccag aaagaaagcc caactagatc ctcaqaanac
                                                                     360
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgccccc gtctgttatg
                                                                     420
atttctctcc attgcagcna naaacccgtt cttctaagca aacncaggtg atgatggcna
                                                                     480
aaatacaccc cctcttgaag naccnggagg a
                                                                     511
     <210> 73 ·
     <211> 499.
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(499)
     \langle 223 \rangle n = A,T,C or G
     <400> 73
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                                                                     60
cagtggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc
                                                                    120
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctccta
                                                                    180
caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc agggtgcatc
                                                                    240
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca
                                                                    300
360
antctagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgccagc
                                                                    420
catctgttgt ttgcccctcc cccgntgcct tccttgaccc tggaaagtgc cactcccact
                                                                    480
gtcctttcct aantaaaat
                                                                    499
     <210> 74
     <211> 537
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(537)
     <223> n = A,T,C or G
     <400> 74
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat
                                                                     60
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ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact
                                                                       120
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa
                                                                       180
cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga
                                                                       240
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaaatgg taatcattag
                                                                       300
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc
                                                                       360
cagtttgctt gatatatttg ttgatattaa gattcttgac ttatattttg aatgggttct
                                                                       420
actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat
                                                                       480
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt
                                                                       537
      <210> 75
      <211> 467
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(467)
      <223> n = A,T,C or G
      <400> 75
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc
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tgcatattac acgtacctcc tcctgctcct caagtagtgt ggtctatttt gccatcatca
                                                                       120
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg
                                                                       180
tggcacaagg aggccatctt ttcctcatcg gttattgtcc ctagaagcgt cttctgagga
                                                                       240
tctagttggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta
                                                                       300
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa
                                                                       360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc
                                                                       420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn
                                                                       467
      <210> 76
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(400)
      <223> n = A,T,C or G
      <400> 76
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctcgcgctac
                                                                       60
tetetettte tggeetggag getatecage gtactecaaa gatteaggtt tacteaegte
                                                                       120
atccagcaga gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat
                                                                      180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaaqtq qaqcattcaq
                                                                      240
actigiciti cagcaaggac iggicitici atcicitgia ciacactgaa iicacccca
                                                                      300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng
                                                                      360
ttnagtggga tcganacatg taagcagcan catgggaggt
                                                                      400
      <210> 77
      <211> 248
      <212> DNA
      <213> Homo sapien
      <400> 77
ctggagtgcc ttggtgtttc.aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                       60
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ccagctgccc cggcggggga tgcgaggctc ggagcaccct tgcccggctg tgattgctgc
                                                                        120
caggeactgt teateteage ttttetgtee etttgeteec ggeaageget tetgetgaaa
                                                                        180
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa
                                                                        240
aaaaaaa
                                                                        248
      <210> 78
      <211> 201
      <212> DNA
      <213> Homo sapien
      <400> 78
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                         60
tcacccagac cccgccctgc ccgtgcccca cgctgctgct aacgacagta tgatgcttac
                                                                        120
totgotacto ggaaactatt tttatgtaat taatgtatgo tttottgttt ataaatgcot
                                                                        180
gatttaaaaa aaaaaaaaaa a
                                                                        201
      <210> 79
      <211> 552
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(552)
      \langle 223 \rangle n = A,T,C or G
      <400> 79
tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg
                                                                         60
tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt
                                                                        120
cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag
                                                                        180
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt
                                                                        240
atgcaagtta gtaattactc agggttaact aaattacttt aatatgctqt tqaacctact
                                                                        300
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga
                                                                        360
taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tqqaatttta
                                                                        420
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac
                                                                        480
cngttttggt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa
                                                                        540
aaaaaaaaa aa
                                                                        552
      <210> 80
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(476)
      \langle 223 \rangle n = A,T,C or G
      <400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga
                                                                         60
ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct
                                                                        120
cacacagact cocgagtage tgggactaca ggcacacagt cactgaagca qqccctqttt
                                                                        180
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta
                                                                        240
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac
                                                                        300
tettetaagt cetetteeag ceteaetttg agteeteett gggggttgat aggaantnte
                                                                        360
```

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tettggettt eteaataaaa tetetateea teteatgttt aatttggtae gentaaaaat
                                                                       420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaa aaaaaaaaa aaaaaa
                                                                       476
      <210> 81
      <211> 232
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(232)
      <223> n = A,T,C or G
      <400> 81
tttttttttg tatgeenten etgtggngtt attgttgetg ceaccetgga ggageceagt
                                                                        60
ttettetgta tetttettt etgggggate tteetggete tgeceeteea tteeeageet
                                                                       120
ctcatcccca tcttgcactt ttgctagggt tggaggcgct ttcctggtag cccctcagag
                                                                       180
actcagtcag cgggaataag tcctaggggt ggggggtgtg gcaagccggc ct
                                                                       232
      <210> 82
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(383)
      <223> n = A,T,C or G
      <400> 82
aggegggage agaagetaaa gecaaageee aagaagagtg geagtgeeag caetggtgee .
                                                                        60
agtaccagta ccaataacat gccagtgcca gtgccagcac cagtggtggc ttcaqtqctq
                                                                       120
gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg
                                                                       180
ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt
                                                                       240
gttaatcctg ccagtctttc tcttcaagcc agggtgcatc ctcagaaacc tactcaacac
                                                                       300
agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg
                                                                       360
ccatttcaaa aaaaaaaaaa aaa
                                                                       383
      <210> 83
      <211> 494
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(494)
      <223> n = A,T,C or G
      <400> 83
accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca
                                                                        60
gggagatcga gtctatacgc tgaagaaatt tgacccgatg ggacaacaga cctgctcagc
                                                                       120
ccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa
                                                                       180
acgetteaag gtgeteatga ceeageaace gegeeetgte etetgagggt cettaaactg
                                                                       240
atgtetttte tgeeacetgt tacceetegg agaeteegta accaaactet teggaetgtg
                                                                       300
agecetgatg cettitigee agecatacie titiggeniee agtetetegt ggegatigat
                                                                       360
```

ι.

```
tatgcttgtg tgaggcaatc atggtggcat cacccatnaa gggaacacat ttgantttt
                                                                        420
tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta
                                                                        480
aaaaaaaaa aaaa
                                                                        494
      <210> 84
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(380)
      <223> n = A, T, C or G
      <400> 84
gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca
                                                                         60
agtatectge geogegtett etacegteee tacetgeaga tettegggea gatteeceag
                                                                        120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg
                                                                        180
gcacaccete etggggecea ggegggeace tgegtetece agtatgecaa etggetggtg
                                                                        240
gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg
                                                                        300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc
                                                                        360
agcgttnccg cctcatccgg
                                                                        380
      <210> 85
      <211> 481
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(481)
      <223> n = A,T,C or G
      <400> 85
gagttagete etecacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
                                                                        60
tnccatcgtc atactgtagg tttgccacca cctcctgcat cttggggcgg ctaatatcca
                                                                        120
ggaaactctc aatcaagtca ccgtcnatna aacctgtggc tggttctgtc ttccgctcgg
                                                                        180
tgtgaaagga tctccagaag gagtgctcga tcttccccac acttttgatg actttattga
                                                                        240
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagtgag gtcaccagcc
                                                                        300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggt gnagtctcac
                                                                        360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa
                                                                        420
aaagaacacc tcctggaagt gctngccgct cctcgtccnt tggtggnngc gcntnccttt
                                                                        480
                                                                        481
      <210> 86
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(472)
      \langle 223 \rangle n = A,T,C or G
      <400> 86
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aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt
                                                                        60
acttggaaaa gcaacttnaa gcctggacac tggtattaaa attcacaata tqcaacactt
                                                                       120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taaqqqtatq
                                                                       180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct tttttttga
                                                                       240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt
                                                                       300
catgggacag agccatttga tttaaaaaagc aaattgcata atattgagct ttgggagctg
                                                                       360
atatntgage ggaagantag cetttetaet teaccagaca caacteettt catattqqqa
                                                                       420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg
                                                                       472
      <210> 87
      <211> 413
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(413)
      <223> n = A,T,C or G
      <400> 87
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                       60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaaqcttatq
                                                                       120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatqtc ttqqqqacct
                                                                       180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                      240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg
                                                                      300
ggggacaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa
                                                                      360
acagaaattg ggtngtatat tgaaananng catcattnaa acgttttttt ttt
                                                                      413
      <210> 88
      <211> 448
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(448)
      <223> n = A,T,C or G
      <400> 88
cgcagcgggt cctctctatc tagctccagc ctctcgcctg ccccactccc cgcgtcccgc
                                                                       60
gtcctagccn accatggccg ggcccctgcg cgccccgctg ctcctgctgg ccatcctggc
                                                                      120
cgtggccctg gccgtgagcc ccgcggccgg ctccagtccc ggcaagccgc cgcgcctggt
                                                                      180
gggaggccca tggaccccgc gtggaagaag aaggtgtgcg gcgtgcactg gactttgccg
                                                                      240
teggenanta caacaaacce geaacnactt ttacenagen egegetgeag gttgtgeege
                                                                      300
cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng
                                                                      360
tttaccagaa ccnagccaat tngaacaatt ncccctccat aacagcccct tttaaaaaqq
                                                                      420
gaancantcc tgntcttttc caaatttt
                                                                      448
      <210> 89
      <211> 463
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
```

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<222> (1)...(463)
      <223> n = A,T,C or G
      <400> 89
gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gaqtttatca
                                                                        60
gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatqtca aaaaattagc
                                                                       120
agaggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtt
                                                                       180
ctcagtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttqcatc
                                                                       240
tttnatgttn agacttgcct ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg
                                                                       300
tttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn
                                                                       360
aattetete ceatannaaa acceangeee ttggganaat ttgaaaaang gnteettenn
                                                                       420
aattonnana anttoagntn toatacaaca naacnggano coc
                                                                       463
      <210> 90
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(400)
      <223> n = A,T,C or G
      <400> 90
agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt
                                                                        60
cttccactca ctgtctgtaa gcntnttaac ccagactgta tcttcataaa taqaacaaat
                                                                       120
tetteaceag teacatette taggacettt ttggatteag ttagtataag etetteeact
                                                                       180
tcctttgtta agacttcatc tggtaaagtc ttaagttttg tagaaaggaa tttaattqct
                                                                       240
cgttctctaa caatgtcctc tccttgaagt atttggctga acaacccacc tnaagtccct
                                                                       300
ttgtgcatcc attttaaata tacttaatag ggcattggtn cactaggtta aattctqcaa
                                                                       360
gagtcatctg tctgcaaaag ttgcgttagt atatctgcca
                                                                       400
      <210> 91
      <211> 480
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(480)
      <223> n = A,T,C \text{ or } G
      <400> 91
gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact
                                                                        60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                       120
atgeetettt gaetaeegtg tgeeagtget ggtgattete acacacetee nneegetett
                                                                       180
tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaaat tcacccacga
                                                                       240
gacacttgaa aggtgtaaca aagcgactct tgcattgctt tttgtccctc cggcaccagt
                                                                       300
tgtcaatact aaccegetgg tttgcctcca tcacatttgt gatctgtagc tctggataca
                                                                       360
tctcctgaca gtactgaaga acttcttctt ttgtttcaaa agcaactctt ggtgcctgtt
                                                                       420
ngatcaggtt cccatttccc agtccgaatg ttcacatggc atatnttact tcccacaaaa
                                                                       480
      <210> 92
      <211> 477
      <212> DNA
```

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<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(477)
      <223> n = A,T,C \text{ or } G
      <400> 92
atacagecca nateceacca egaagatgeg ettgttgaet gagaacetga tgeggteaet
                                                                         60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt
                                                                         120
cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggt
                                                                         180
taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccgact gtgcgggacc
                                                                         240
tgcagcgaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca
                                                                         300
gaacetteeg cetgttetet ggegteacet geagetgetg cegetnacae teggeetegg
                                                                         360
accageggae aaaeggegtt gaacageege aceteaegga tgeecantgt gtegegetee
                                                                         420
aggaacggcn ccagcgtgtc caggtcaatg tcggtgaanc ctccgcgggt aatggcg
                                                                         477
      <210> 93
      <211> 377
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(377)
      \langle 223 \rangle n = A,T,C or G
      <400> 93
gaacggctgg accttgcctc gcattgtgct gctggcagga ataccttggc aagcagctcc
                                                                         60
agteegagea geceeagace getgeegeee gaagetaage etgeetetgg cetteegete
                                                                        120
cgcctcaatg cagaaccant agtgggagca ctgtgtttag agttaagagt gaacactgtn
                                                                        180
tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaat ttccaaacaa
                                                                        240
caacaacaaa ataacatgtt tgcctgttna gttgtataaa agtangtgat tctgtatnta
                                                                        300
aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa
                                                                        360
ataaatatat tattaaa
                                                                        377
      <210> 94
      <211> 495
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(495)
      \langle 223 \rangle n = A,T,C or G
      <400> 94
ccctttgagg ggttagggtc cagttcccag tggaagaaac aggccaggag aantgcgtgc
                                                                         60
cgagctgang cagatttccc acagtgaccc cagagccctg ggctatagtc tctgacccct
                                                                        120
ccaaggaaag accaccttct ggggacatgg gctggagggc aggacctaga ggcaccaagg
                                                                        180
gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgccccc
                                                                        240
acgaggaana ggccctgant cctgggatca nacacccctt cacgtgtatc cccacacaaa
                                                                        300
tgcaagetca ccaaggteee eteteagtee etteectaca ecetgaacgg neactggeee
                                                                        360
acacccaccc agancancca cccgccatgg ggaatgtnct caaggaatcg cngggcaacg
                                                                        420
tggactctng tcccnnaagg gggcagaatc tccaatagan gganngaacc cttgctnana
                                                                        480
```

```
aaaaaaana aaaaa
                                                                         495
      <210> 95
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(472)
      \langle 223 \rangle n = A,T,C or G
      <400> 95
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc
                                                                         60
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt
                                                                        120
tagctgtttt gagttgattc gcaccactgc accacaactc aatatgaaaa ctatttnact
                                                                        180
tatttattat cttgtgaaaa gtatacaatg aaaattttgt tcatactgta tttatcaagt
                                                                        240
atgatgaaaa gcaatagata tatattcttt tattatgttn aattatgatt gccattatta
                                                                        300
atcggcaaaa tgtggagtgt atgttctttt cacagtaata tatgcctttt gtaacttcac
                                                                        360
ttggttattt tattgtaaat gaattacaaa attcttaatt taagaaaatg gtangttata
                                                                        420
tttanttcan taatttcttt ccttgtttac gttaattttg aaaagaatgc at
                                                                        472
      <210> 96
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (476)
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<400> 111 agccaggcgt coctotgcot goccactcag tggcaacacc cgggagctgt tttgtccttt 60 gtggagcctc agcagttccc tctttcagaa ctcactgcca agagccctga acaggagcca 120 ccatgcagtg cttcagcttc attaagacca tgatgatcct cttcaatttg ctcatctttc 180 tgtgtggtgc agccctgttg gcagtgggca tctgggtgtc aatcgatggg gcatcctttc 240 tgaagatett egggeeactg tegteeagtg ceatgeagtt tgteaacgtg ggetaettee 300 tcatcgcagc cggcgttgtg gtctttgctc ttggtttcct gggctgctat ggtgctaaga 360 ctgagagcaa gtgtgccctc gtgacgttct tcttcatcct cctcctcatc ttcattgctg 420 aggttgcagc tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctqacqt 480 tgctggtagt gcctgccatc aagaaagatt atggttccca ggaagacttc actcaagtgt 540 ggaacaccac catgaaaggg ctcaagtgct gtggcttcac caactatacg gattttgagg 600 actcacccta cttcaaagag aacagtgcct ttcccccatt ctgttgcaat gacaacgtca 660 ccaacacagc caatgaaacc tgcaccaagc aaaaggctca cgaccaaaaa gtagagggtt 720 getteaatea gettttgtat gacateegaa etaatgeagt caeegtgggt ggtgtggeag 780 ctggaattgg gggcctcgag ctggctgcca tgattgtgtc catgtatctg tactgcaatc 840 tacaataagt ccacttetge etetgecaet actgetgeca catgggaact gtgaagagge 900 accetggeaa geageagtga ttgggggagg ggacaggate taacaatgte acttgggeea 960 gaatggacct gccctttctg ctccagactt ggggctagat agggaccact ccttttagcg 1020 atgcctgact ttccttccat tggtgggtgg atgggtgggg ggcattccag agcctctaag 1080 gtagccagtt ctgttgccca ttcccccagt ctattaaacc cttgatatgc cccctaggcc 1140 tagtggtgat cccagtgctc tactggggga tgagagaaag gcattttata gcctgggcat 1200 aagtgaaatc agcagagcct ctgggtggat gtgtagaagg cacttcaaaa tgcataaacc 1260 tgttacaatg ttaaaaaaaa aaaaaaaaa 1289

<210> 112

<211> 315

<212> PRT

<213> Homo sapien

<400> 112

Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val Asn Lys Gln 10 Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys Asp Val Phe 20 25 Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr Gly Val Ala -40 Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro Ser Ile Leu Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly Gln Ile Pro 70 75 Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn Cys Ser Ser 85 90 Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala Gly Thr Cys 105 Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu Leu Val Ile Phe 120 Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu Leu Ile Ala Met Phe 135 140 Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys 150 155 Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu 165 170 Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Leu Arg Gln 185 Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu

195 200 His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr 215 220 Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp 230 235 Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val 245 250 Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg 265 Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly 280 Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly 290 295 Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp 310

<210> 113

<211> 553

<212> PRT

<213> Homo sapien

<400> 113

Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala 10 Gln Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu 20 25 Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Glu Val Gly Val 40 Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly 70 75 Arg Tyr Gly Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile 90 Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu 105 Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly 120 Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu 135 140 Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala 150 155 Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr 170 Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu 185 Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu 200 Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly 215 220 Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His 230 235 Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu 250 Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg

260 265 Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe 280 Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val 295 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly 310 315 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu 330 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg 340 345 Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala 360 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu 375 380 Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala 390 395 Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly 405 410 Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu 420 425 Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala 440 Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser 455 Ala Cys Asp Val Ser Val Arg Val Val Gly Glu Pro Thr Glu Ala 470 475 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp 490 Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser 505 Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala 520 Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp 535 Lys Ser Asp Leu Ala Lys Tyr Ser Ala 545

<210> 114

<211> 241

<212> PRT

<213> Homo sapien

<400> 114

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46

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90
Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr
            100
                                105
                                                     110
Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys
        115
                            120
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
    130
                        135
                                            140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
145
                    150
                                        155
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
                165
                                    170
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
                                185
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
                            200
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
                        215
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
225
                    230
                                        235
Gln
      <210> 115
      <211> 366
      <212> DNA
      <213> Homo sapien
      <400> 115
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cattleactg tgatgtatat tgtgttgcaa aaaaaaaaaa gtgtctttgt ttaaaattac
                                                                       120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctqa
                                                                       180
actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggtga attggatggt
                                                                       240
totcagaacc atttcaccca gacagcotgt ttotatcctg tttaataaat tagtttgggt
                                                                       300
tctctacatg cataacaaac cctgctccaa tctgtcacat aaaagtctgt gacttgaagt
                                                                       360
ttagtc
                                                                       366
      <210> 116
      <211> 282
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(282)
      <223> n = A,T,C or G
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                                                                       60
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa
                                                                      120
agactttact attttcatat tttaagacac atgatttatc ctattttagt aacctggttc
                                                                      180
atacgttaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt
                                                                      240
tcaatcinga actaictana tcacagacat tictaticci ti
                                                                      282
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<210> 117

<211> 305

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<212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(305)
      <223> n = A,T,C or G
      <400> 117
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                                                                         60
tatttatcct ccctcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa
                                                                        120
aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga
                                                                        180
tactgatccc tgatcactgt cctaatgcag gatgtgggaa acagatgagg tcacctctgt
                                                                        240
gactgcccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat
                                                                        300
tgggt
                                                                        305
      <210> 118
      <211> 71
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(71)
      <223> n = A,T,C or G
      <400> 118
accaaggtgt ntgaatctct gacgtgggga tctctgattc ccgcacaatc tgagtggaaa
                                                                         60
aantcctggg t
                                                                         71
      <210> 119
      <211> 212
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(212)
      <223> n = A,T,C \text{ or } G
      <400> 119
actccggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca
                                                                         60
gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac
                                                                        120
agtaagctgg cccttctaat aaaagaaaat tgaaaggttt ctcactaanc ggaattaant
                                                                        180
aatggantca aganactccc aggcctcagc gt
                                                                        212
      <210> 120
      <211> 90
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(90)
      <223> n = A, T, C or G
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<400> 120 actogitigoa natcaggggo coccoagagi cacogitigoa ggagitocito iggiotitgoo 60 ctccgccggc gcagaacatg ctggggtggt 90 <210> 121 <211> 218 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(218) <223> n = A,T,C or G<400> 121 tgtancgtga anacgacaga nagggttgtc aaaaatggag aanccttgaa gtcattttga 60 gaataagatt tgctaaaaga tttggggcta aaacatggtt attgggagac atttctgaag 120 atatncangt aaattangga atgaattcat ggttcttttg ggaattcctt tacgatngcc 180 agcatanact tcatgtgggg atancagcta cccttgta 218 <210> 122 <211> 171 <212> DNA <213> Homo sapien <400> 122 taggggtgta tgcaactgta aggacaaaaa ttgagactca actggcttaa ccaataaagg 60 catttgttag ctcatggaac aggaagtcgg atggtggggc atcttcagtg ctgcatgagt 120 caccaccccg gcggggtcat ctgtgccaca ggtccctgtt gacagtgcgg t 171 <210> 123 <211> 76 <212> DNA <213> Homo sapien <220> <221> misc\_feature <222> (1)...(76) <223> n = A, T, C or G<400> 123 tgtagcgtga agacnacaga atggtgtgtg ctgtgctatc caggaacaca tttattatca 60 ttatcaanta ttgtgt 76 <210> 124 <211> 131 <212> DNA <213> Homo sapien <400> 124 acctttcccc aaggccaatg tcctgtgtgc taactggccg gctgcaggac agctgcaatt 60 caatgtgctg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg 120 ttaagatttg t 131

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<210> 125
      <211> 432
      <212> DNA
      <213> Homo sapien
      <400> 125
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                                                                        60
cttgaaaaag aggtgatagc tcttcagagg acttgtgact tttgctcaga tgctgaagaa
                                                                       120
ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat
                                                                       180
ttgcctcacc aaacaaaagt gaaacaactg agagaaaatt ttcaggaaaa aagacagtgg
                                                                       240
ctcttgaagt atcagtcact tttgagaatg tttcttagtt actgcatact tcatggatcc
                                                                       300
catggtgggg gtcttgcatc tgtaagaatg gaattgattt tgcttttgca agaatctcag
                                                                       360
caggaaacat cagaaccact attttctagc cctctgtcag agcaaacctc agtgcctctc
                                                                       420
ctctttgctt gt
                                                                       432
      <210> 126
      <211> 112
      <212> DNA
      <213> Homo sapien
      <400> 126
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                                                                        60
agtaagaatg atatttcccc ccagggatca ccaaatattt ataaaaattt gt
                                                                       112
      <210> 127
      <211> 54
      <212> DNA
      <213> Homo sapien
      <400> 127
accacgaaac cacaaacaag atggaagcat caatccactt gccaagcaca gcag
                                                                        54
      <210> 128
      <211> 323
      <212> DNA
      <213> Homo sapien
      <400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc
                                                                        60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca
                                                                       120
ttctctctga agtctaggtt acccattttg gggacccatt ataggcaata aacacagttc
                                                                       180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcctttt tcttagcctt
                                                                       240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct
                                                                       300
aggctgcctt cttttccatg tcc
                                                                       323
      <210> 129
      <211> 192
      <212> DNA
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      <220>
      <221> misc_feature
      <222> (1)...(192)
      <223> n = A,T,C \text{ or } G
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                                                                          60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc
                                                                         120
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg
                                                                         180
gataaacaaa gt
                                                                         192
      <210> 130
      <211> 362
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(362)
      \langle 223 \rangle n = A,T,C or G
      <400> 130
ccctttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca
                                                                         60
tataatgacg caacaaaaag gtgctgttta.gtcctatggt tcagtttatg cccctgacaa
                                                                         120
gtttccattg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa
                                                                         180
ttotgtatto cattttgtta acgootggta gatgtaacot gotangaggo taactttata
                                                                         240
cttatttaaa agetettatt ttgtggteat taaaatggea atttatgtge ageaetttat
                                                                         300
tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaatctta aaaagtaatg
                                                                        360
gg
                                                                        362
      <210> 131
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (332)
      \langle 223 \rangle n = A,T,C or G
      <400> 131
ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca
                                                                         60
gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga
                                                                        120
gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc
                                                                        180
ttctgaacta gattaaggca gcttgtaaat ctgatgtgat ttggtttatt atccaactaa
                                                                        240
cttccatctg ttatcactgg agaaagccca gactccccan gacnggtacg gattgtgggc
                                                                        300
atanaaggat tgggtgaagc tggcgttgtg gt
                                                                        332
      <210> 132
      <211> 322
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(322)
      <223> n = A, T, C or G
      <400> 132
actititgcca tititgtatat ataaacaatc tigggacatt ciccigaaaa ciaggigtcc
                                                                         60
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agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat
                                                                         120
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt
                                                                         180
tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg
                                                                         240
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct
                                                                         300
gtaacaatct acaattggtc ca
                                                                         322
      <210> 133
      <211> 278
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      <220>
      <221> misc_feature
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      <400> 133
acaagccttc acaagtttaa ctaaattggg attaatcttt ctgtanttat ctgcataatt
cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta
                                                                         120
ctatttaaaa aaaatcacaa atctttccct ttaagctatg ttnaattcaa actattcctg
                                                                         180
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt
                                                                         240
cccacgaaac actaataaaa accacagaga ccagcctg
                                                                        278
      <210> 134
      <211> 121
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(121)
      \langle 223 \rangle n = A,T,C or G
      <400> 134
gtttanaaaa cttgtttagc tccatagagg aaagaatgtt aaactttgta ttttaaaaca
                                                                         60
tgattctctg aggttaaact tggttttcaa atgttatttt tacttgtatt ttgcttttgg
                                                                        120
                                                                        121
      <210> 135
      <211> 350
      <212> DNA
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      <220>
      <221> misc_feature
      <222> (1)...(350)
      <223> n = A,T,C or G
      <400> 135
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctatacc
                                                                         60
atancaagtg gtgactggtt aagcgtgcga caaaggtcag ctggcacatt acttgtgtgc
                                                                        120
aaacttgata ettttgttet aagtaggaae tagtataeag tneetaggan tggtaeteea
                                                                        180
gggtgccccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct
                                                                        240
ccacctcaat caagecetgg gecatgetac etgeaattgg etgaacaaac gtttgetgag
                                                                        300
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt
                                                                        350
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<210> 136
      <211> 399
      <212> DNA
      <213> Homo sapien
      <220>
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      <222> (1)...(399)
      <223> n = A,T,C or G
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                                                                         60
gctgtgattg tatccgaata ntcctcgtga gaaaagataa tgagatgacg tgagcagcct
                                                                        120
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga
                                                                       180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag
                                                                       240
aaaactgcag aggcccaggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc
                                                                       300
teccaggaac cegggeaaag gecateecea cetacageca geatgeecac tggegtgatg
                                                                       360
ggtgcagang gatgaagcag ccagntgttc tgctgtggt
                                                                       399
      <210> 137
      <211> 165
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      <223> n = A,T,C or G
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                                                                        60
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga
                                                                       120
ttggctggtc ccactggtgg tcactgtcat tggtggggtt cctgt
                                                                       165
      <210> 138
      <211> 338
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(338)
      \langle 223 \rangle n = A,T,C or G
      <400> 138
actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc
                                                                        60
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa
                                                                       120
tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg
                                                                       180
tcatgtgttt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt
                                                                       240
cangecteag gaageeteaa gtteeattea getttgeeae tgtacattee ecatntttaa
                                                                       300
aaaaactgat gccttttttt tttttttttg taaaattc
                                                                       338
      <210> 139
      <211> 382
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      <400> 139
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                                                                         60
gaaagggact tcgagtaaga aggtgattta cagccagcct agtgcccgaa gtgaaggaga
                                                                        120
attcaaacag acctcgtcat tcctggtgtg agcctggtcg gctcaccgcc tatcatctgc
                                                                        180
atttgcctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg
                                                                        240
ccttatttgt cttctacacc ccacagggcc ccctacttct tcggatgtgt ttttaataat
                                                                        300
gtcagctatg tgccccatcc tecttcatgc cctccctccc tttcctacca ctgctgagtg
                                                                        360
gcctggaact tgtttaaagt gt
                                                                        382
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      <211> 200
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(200)
      \langle 223 \rangle n = A,T,C or G
      <400> 140
accaaanctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat
                                                                        60
actittcatt taacanctit tgttaagtgt caggctgcac tttgctccat anaattattg
                                                                        120
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatttt
                                                                        180
atattcagca taaaggagaa
                                                                        200
      <210> 141
      <211> 335
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(335)
      <223> n = A,T,C or G
      <400> 141
actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg
                                                                        60
gggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc agggtttgtt
                                                                       120
atgcatgtag agaacccaaa ctaatttatt aaacaggata gaaacaggct gtctgggtga
                                                                       180
aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg
                                                                       240
tttttctacc agttcagaga tnggttaatg actanttcca atggggaaaa agcaagatgg
                                                                       300
attcacaaac caagtaattt taaacaaaga cactt
                                                                       335
      <210> 142
      <211> 459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(459)
      <223> n = A,T,C or G
```

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<400> 142
accaggitaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta
                                                                        60
gggttgttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat
                                                                       120
ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc agtctgatca
                                                                       180
cacatggtcc aacaacactc aaataataaa tcaaatatna tcagatgtta aagattggtc
                                                                       240
ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccgaca taaaaccaca
                                                                       300
tcaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga
                                                                       360
agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct
                                                                       420
cagcangggt gggaggaacc agctcaacct tggcgtant
                                                                       459
      <210> 143
      <211> 140
      <212> DNA
      <213> Homo sapien
      <400> 143
acattteett ceaceaagte aggaeteetg gettetgtgg gagttettat cacetgaggg
                                                                        60
aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctgag
                                                                       120
accatccgac ttccctgtgt
                                                                       140
      <210> 144
      <211> 164
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(164)
      <223> n = A,T,C or G
      <400> 144
acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct
                                                                        60
atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaatttg
                                                                       120
aggcaattaa tccatatttg ttttcaataa ggaaaaaaag atgt
                                                                       164
      <210> 145
      <211> 303
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(303)
      <223> n = A,T,C or G
      <400> 145
acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa
                                                                       60
actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat
                                                                       120
gcaggacage tatcataagt eggeccagge atceagatac taccatttgt ataaacttca
                                                                       180
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag
                                                                       240
tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat
                                                                      300
caa
                                                                      303
```

<210> 146

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<211> 327
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(327)
      <223> n = A,T,C or G
      <400> 146
actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac
                                                                        60
actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttgc caacaggcct
                                                                       120
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt
                                                                       180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc
                                                                       240
agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg
                                                                       300
taggggtgag ctgtgtgact ctatggt
                                                                       327
      <210> 147
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(173)
      <223> n = A,T,C or G
      <400> 147
acattgtttt tttgagataa agcattgana gagctctcct taacgtgaca caatggaagg
                                                                       60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                      120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt
                                                                      173
      <210> 148
      <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(477)
      <223> n = A, T, C or G
acaaccactt tatctcatcg aatttttaac ccaaactcac tcactgtgcc tttctatcct
                                                                       60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact
                                                                      120
gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg
                                                                      180
gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac
                                                                      240
nccancecae etcacegace ceatectett acacagetae etcettgete tetaacecea
                                                                      300
tagattatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag
                                                                      360
caccactggt aagcettete cagecaacae acacacae acacneacae acacacatat
                                                                      420
ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg
                                                                      477
      <210> 149
      <211> 207
      <212> DNA
```

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<213> Homo sapien
      <400> 149
acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac
                                                                         60
taacgtattt tagagagcca aggaaggttt ctgtggggag tgggatgtaa ggtggggcct
                                                                        120
gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca
                                                                        180
tttcaggcag agggaacagc agtgaaa
                                                                        207
      <210> 150
      <211> 111
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(111)
      <223> n = A, T, C \text{ or } G
      <400> 150
accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg
                                                                         60
cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t
                                                                        111
      <210> 151
      <211> 196
      <212> DNA
      <213> Homo sapien
      <400> 151
agcgcggcag gtcatattga acattccaga tacctatcat tactcgatgc tgttgataac
                                                                         60
agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat
                                                                        120
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggtccccac tgtctacgag
                                                                        180
gtgcatccgg ctcagt
                                                                        196
      <210> 152
      <211> 132
      <212> DNA
      <213> Homo sapien
      <400> 152
acagcacttt cacatgtaag aagggagaaa ttcctaaatg taggagaaag ataacagaac
                                                                         60
cttccccttt tcatctagtg gtggaaacct gatgctttat gttgacagga atagaaccag
                                                                        120
gagggagttt gt
                                                                        132
      <210> 153
      <211> 285
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (285)
      \langle 223 \rangle n = A,T,C or G
      <400> 153
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag
                                                                        60
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```
cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcagcagga
                                                                       120
gcacatcaat aaagtccaaa gtcttggact tggccttggc ttgqaqqaaq tcatcaacac
                                                                       180
cctggctagt gagggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca
                                                                       240
gtctgcaggc cctgtggaag cgccgtccac acggagtnag qaatt
                                                                       285
      <210> 154
      <211> 333
      <212> DNA
      <213> Homo sapien
      <400> 154
accacagtcc tgttgggcca gggcttcatg accctttctg tgaaaagcca tattatcacc
                                                                        60
accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac
                                                                       120
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcctg
                                                                       180
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctgatttg
                                                                       240
agtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat ccggagaatg
                                                                       300
gtcaggcctg tctcatccat atggatcttc cqq
                                                                       333
      <210> 155
      <211> 308
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(308)
      <223> n = A,T,C or G
      <400> 155
actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg
                                                                        60
gaaagtgctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat
                                                                       120
ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag ccccagcccc
                                                                       180
atcacagete actgetetgt teatecagge ceageatgta gtggetgatt ettettgget
                                                                       240
gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcatgctg
                                                                       300
gccctggt
                                                                       308
      <210> 156
      <211> 295
      <212> DNA
      <213> Homo sapien
      <400> 156
accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta
                                                                       60
ttattgatta ctgagagaac tgttagacat ttagttgaag attttctaca caggaactga
                                                                      120
gaataggaga ttatgtttgg ccctcatatt ctctcctatc ctccttgcct cattctatgt
                                                                      180
ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat
                                                                      240
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat
                                                                      295
      <210> 157
      <211> 126
      <212> DNA
      <213> Homo sapien
      <400> 157
acaagtttaa atagtgctgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct
                                                                       60
```

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gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc
                                                                       120
cttagt
                                                                       126
      <210> 158
      <211> 442
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(442)
      <223> n = A,T,C or G
      <400> 158
acceactggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg
                                                                       60
aanccagcag gctgccccta gtcagtcctt ccttccagag aaaaagagat ttgagaaagt
                                                                       120
gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatattt
                                                                       180
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc caqtqaaqta
                                                                       240
natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtggtg
                                                                       300
ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga
                                                                       360
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg
                                                                       420
tgttcattct ctgatgtcct gt
                                                                       442
      <210> 159
      <211> 498
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(498)
      <223> n = A,T,C or G
      <400> 159
acttccaggt aacgttgttg tttccgttga gcctgaactg atgggtgacg ttgtaggttc
                                                                       60
tccaacaaga actgaggttg cagagcgggt agggaagagt gctgttccag ttgcacctgg
                                                                      120
gctgctgtgg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag
                                                                      180
gtgtgttgtt gganttgagc tcgggcggct gtggtaggtt gtgggctctt caacaggggc
                                                                      240
tgctgtggtg ccgggangtg aangtgttgt gtcacttgag cttggccagc tctggaaagt
                                                                      300
antanattct tcctgaaggc cagcgcttgt ggagctggca ngggtcantg ttgtgtqtaa
                                                                      360
cgaaccagtg ctgctgtggg tgggtgtana tcctccacaa agcctgaagt tatggtgtcn
                                                                      420
tcaggtaana atgtggtttc agtgtccctg ggcngctgtg gaaggttgta nattgtcacc
                                                                      480
aagggaataa gctgtggt
                                                                      498
      <210> 160
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (380)
      <223> n = A,T,C or G
      <400> 160
```

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acctgcatcc agcttccctg ccaaactcac aaggagacat caacctctag acagggaaac
                                                                         60
agetteagga tactteeagg agacagagee accageagea aaacaaatat teecatgeet
                                                                        120
ggagcatggc atagaggaag ctganaaatg tggggtctga ggaagccatt tgagtctggc
                                                                        180
cactagacat ctcatcagcc acttgtgtga agagatgccc catgacccca gatgcctctc
                                                                        240
ccaccettac etecatetca cacacttgag etttecacte tgtataatte taacateetg
                                                                        300
gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggctgatt tctaacgaaa
                                                                        360
cttgtagaat gaagcctgga
                                                                        380
      <210> 161
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 161
actocacate coetetgage aggoggttgt cgttcaaggt gtatttggcc ttgcctgtca
                                                                        60
cactgtccac tggcccctta tccacttggt gcttaatccc tcgaaagagc atgt
                                                                        114
      <210> 162
      <211> 177
      <212> DNA
      <213> Homo sapien
      <400> 162
actttctgaa tcgaatcaaa tgatacttag tgtagtttta atatcctcat atatatcaaa
                                                                         60
gttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt
                                                                        120
tggtgatata taacttggca ataacccagt ctggtgatac ataaaactac tcactgt
                                                                        177
      <210> 163
      <211> 137
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(137)
      \langle 223 \rangle n = A,T,C or G
      <400> 163
catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac
                                                                         60
canagaaggc agctacggct actcctacat cctggcgtgg gtggccttcg cctgcacctt
                                                                        120
catcagcggc atgatgt
                                                                        137
      <210> 164
      <211> 469
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(469)
      \langle 223 \rangle n = A,T,C or G
      <400> 164
cttatcacaa tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta
                                                                        60
tgcaatgcat catgctattt catacctaat gagggagttc caggagattc aaccaggaaa
                                                                       120
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tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt
                                                                       180
gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg
                                                                       240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg
                                                                       300
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct
                                                                       360
totagtaggo acagggotoc caggocaggo otoattotoc totggootot aatagtoaat
                                                                       420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt
                                                                       469
      <210> 165
      <211> 195
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(195)
      <223> n = A, T, C or G
      <400> 165
acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctggtgg
                                                                        60
atcogotyto atcoactatt cottygotay agtaaaaatt attottatay cocatytooc
                                                                       120
tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact
                                                                       180
tcctctgaga tgagt
                                                                       195
      <210> 166
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(383)
      <223> n = A, T, C or G
      <400> 166
acatcttagt agtgtggcac atcagggggc catcagggtc acagtcactc atagcctcqc
                                                                        60
cgaggtcgga gtccacacca ccggtgtagg tgtgctcaat cttgggcttq qcqcccacct
                                                                       120
ttggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt
                                                                       180
tttgcagacc agcctgagca aggggcggat gttcagcttc agctcctcct tcqtcaqqtq
                                                                       240
gatgccaacc tcgtctangg tccgtgggaa gctggtgtcc acntcaccta caacctgggc
                                                                       300
gangatetta taaagagget eenagataaa etecaegaaa ettetetggg agetgetagt
                                                                       360
nggggccttt ttggtgaact ttc
                                                                       383
      <210> 167
      <211> 247
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(247)
      <223> n = A, T, C or G
      <400> 167
acagagccag accttggcca taaatgaanc agagattaag actaaacccc aagtcganat
                                                                       60
tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc
                                                                       120
```

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tatanccata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac
                                                                        180
tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac
                                                                        240
tgangtc
                                                                        247
      <210> 168
      <211> 273
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(273)
      <223> n = A,T,C or G
      <400> 168
acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa
                                                                         60
aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatgtt tccacaaagg
                                                                        120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc
                                                                        180
aattcccaac ttccttgcca caagettccc aggetttctc ccctggaaaa ctccagettg
                                                                        240
agtcccagat acactcatgg gctgccctgg gca
                                                                        273
      <210> 169
      <211> 431
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(431)
      \langle 223 \rangle n = A,T,C or G
      <400> 169
acageettgg ettececaaa etecacagte teagtgeaga aagateatet teeageagte
                                                                         60
agctcagacc agggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta
                                                                        120
ctactgtcaa atgaccccc atacttcctc aaaggctgtg gtaagttttg cacaggtqaq
                                                                        180
ggcagcagaa agggggtant tactgatgga caccatcttc tctgtatact ccacactgac
                                                                       240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagctc
                                                                       300
acgcacatca ctgacaaccg ggatggaaaa agaantgcca actttcatac atccaactgg
                                                                       360
aaagtgatet gataetggat tettaattae etteaaaage ttetggggge cateagetge
                                                                       420
tcgaacactg a
                                                                       431
      <210> 170
      <211> 266
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(266)
      <223> n = A,T,C or G
      <400> 170
acctgtgggc tgggctgtta tgcctgtgcc ggctgctgaa agggagttca gaggtggagc
                                                                        60
tcaaggagct ctgcaggcat tttgccaanc ctctccanag canagggagc aacctacact
                                                                       120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttggggtg ggcatttgat
                                                                       180
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gtatacttgt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct
                                                                      240
tcaaagctag gggtctggca ggtgga
                                                                      266
      <210> 171
      <211> 1248
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1248)
      \langle 223 \rangle n = A,T,C or G
      <400> 171
ggcagccaaa tcataaacgg cgaggactgc agcccgcact cgcagccctg gcaggcggca
                                                                     60
ctggtcatgg aaaacgaatt gttctgctcg ggcgtcctgg tgcatccgca gtgggtgctg
                                                                     120
teageegeae actitteea gaagtgagtg cagageteet acaccategg getgggeetg
                                                                     180
cacagtettg aggeegacca agageeaggg ageeagatgg tggaggeeag ceteteegta
                                                                     240
cggcacccag agtacaacag accettgete getaacgace teatgeteat caagttggae
                                                                     300
gaatccgtgt ccgagtctga caccatccgg agcatcagca ttgcttcgca gtgccctacc
                                                                     360
gcggggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatqcctacc
                                                                     420
gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac
                                                                     480
ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc
                                                                   540
aacggtgact ctggggggcc cctgatctgc aacgggtact tgcaqqqcct tqtqtctttc
                                                                     600
ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc
                                                                     660
actgagtgga tagagaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa
                                                                     720
attgaccccc aaatacatcc tgcggaagga attcaggaat atctgttccc agcccctcct
                                                                     780
ccctcaggcc caggagtcca ggcccccagc ccctcctccc tcaaaccaag ggtacagatc
                                                                     840
cccagcccct cctccctcag acccaggagt ccagaccccc cagcccctcc tccctcagac
                                                                     900
ccaggagtcc agcccctcct ccctcagacc caggagtcca gacccccag cccctcctcc
                                                                     960
ctcagaccca ggggtccagg cccccaaccc ctcctccctc agactcagag gtccaagccc
                                                                    1020
ccaaccente attecceaga cccagaggte caggteccag ccctentee etcagaccea
                                                                    1080
geggtecaat gecaectaga etnteeetgt acacagtgee eeettgtgge aegttgaeee
                                                                    1140
aaccttacca gttggttttt catttttngt ccctttcccc tagatccaga aataaagttt
                                                                    1200
1248
      <210> 172
      <211> 159
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(159)
      <223> Xaa = Any Amino Acid
      <400> 172
Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
                5
                                   10
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
            20
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
                        55
```

```
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
                    70
                                         75
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
                85
                                    90
Cys Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
            100
                                                     110
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
                            120
                                                125
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
                        135
                                            140
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
145
                    150
      <210> 173
      <211> 1265
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (1265)
      <223> n = A,T,C or G
      <400> 173
ggcagcccgc actcgcagcc ctggcaggcg gcactggtca tggaaaacga attgttctgc
                                                                       60
tegggegtee tggtgeatee geagtgggtg etgteageeg cacactqttt seaqaactee
                                                                       120
tacaccatcg ggctgggcct gcacagtctt gaggccgacc aagagccagg gagccagatg
                                                                       180
gtggaggcca gcctctccgt acggcaccca gagtacaaca gacccttgct cgctaacgac
                                                                       240
ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc
                                                                       300
attgcttcgc agtgccctac cgcggggaac tcttgcctcg tttctggctg gggtctgctg
                                                                       360
gcgaacggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtcctc tgcccagtcg
                                                                       420
cgggggctga cccagagctc tgcgtcccag gcagaatgcc taccgtgctq caqtqcqtqa
                                                                       480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgacccgctg taccacccca
                                                                       540
gcatgttctg.cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg
                                                                       600
ggcccctgat ctgcaacggg tacttgcagg gccttgtgtc tttcggaaaa gccccgtgtg
                                                                       660
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga
                                                                       720
aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac
                                                                       780
atcctgcgga aggaattcag gaatatctgt tcccagcccc tcctccctca ggcccaggag
                                                                       840
tocaggoooc cagoocotco tocotcaaac caagggtaca gatococago coctootco
                                                                       900
tragarreag gagtreagar recreagers etecterete agarreagga gtragers
                                                                       960
tecteentca gacceaggag tecagacece ceagececte eteceteaga eccaggggtt
                                                                     1020
gaggececca acceetecte etteagagte agaggtecaa gececeaace ceteqtteee
                                                                     1080
cagacccaga ggtnnaggtc ccagcccctc ttccntcaga cccagnggtc caatgccacc
                                                                     1140
tagattttcc ctgnacacag tgcccccttg tggnangttg acccaacctt accagttggt
                                                                     1200
ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa
                                                                     1260
aaaaa
                                                                     1265
      <210> 174
      <211> 1459
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc_feature
     <222> (1)...(1459)
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## <223> n = A,T,C or G

## <400> 174 ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctgggcc 60 tgcacagtct tgaggccgac caagagccag ggagccagat ggtggaggcc agcctctccg 120 tacggcaccc agagtacaac agacccttgc tcgctaacga cctcatgctc atcaagttgg 180 acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg caqtgcccta 240 ccgcggggaa ctcttgcctc gtttctggct ggggtctgct ggcgaacggt gagctcacgg 300 gtgtgtgtct gccctcttca aggaggtcct ctgcccagtc gcgggggctg acccagagct 360 ctgcgtccca ggcagaatgc ctaccgtgct gcagtgcgtg aacgtgtcgg tqqtqtctqa 420 ngaggtetge antaagetet atgaceeget gtaceacee ancatgttet gegeeggegg 480 agggcaagac cagaaggact cctgcaacgt gagagaggg aaaggggagg gcaggcgact 540 cagggaaggg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag 600 atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa 660 ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc 720 aqaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt 780 gacctccacc caatagaaaa tcctcttata acttttgact ccccaaaaac ctgactagaa 840 atagcctact gttgacgggg agccttacca ataacataaa tagtcgattt atgcatacgt 900 tttatgcatt catgatatac ctttgttgga attttttgat atttctaagc tacacagttc 960 gtctgtgaat ttttttaaat tgttgcaact ctcctaaaat ttttctgatg tgtttattga 1020 aaaaatccaa gtataagtgg acttgtgcat tcaaaccagg gttgttcaag ggtcaactgt 1080 gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa 1140 aaatcaagac tetacaaaga ggetgggeag ggtggeteat geetgtaate ceageaettt 1200 gggaggcgag gcaggcagat cacttgaggt aaggagttca agaccagcct ggccaaaatq 1260 gtgaaatcct gtctgtacta aaaatacaaa agttagctgg atatggtggc aggcgcctgt 1320 aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt 1380 gaagtgagtt gagatcacac cactatactc cagetggggc aacagagtaa qactetqtet 1440 caaaaaaaa aaaaaaaaa 1459

<210> 175

<211> 1167

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1) ... (1167)

<223> n = A,T,C or G

## <400> 175

gcgcagccct	ggcaggcggc	actggtcatg	gaaaacgaat	tgttctgctc	gggcgtcctg	60
gtgcatccgc	agtgggtgct	gtcagccgca	cactgtttcc'	agaactccta	caccatcggg	120
ctgggcctgc	acagtcttga	ggccgaccaa	gagccaggga	gccagatggt	ggaggccagc	180
ctctccgtac	ggcacccaga	gtacaacaga	ctcttgctcg	ctaacgacct	catgctcatc	240
			accatccgga			300
			tctggctggg			360
			tcggtggtgt			420
			ttctgcgccg			480
			ctgatctgca			540
			cttggcgtgc			600
			gtccagncca			660
			gcggaangaa			720
			gccccagcc			780
			cccaggagtc			840
			cntcagacgc			900

```
cententeeg teagacecag gggtgeagge ecceaacece tenteentea gagteagagg
                                                                       960
tecaageeee caaceeeteg ttececagae ceagaggine aggiceeage ceeteetee
                                                                      1020
tcagacccag cggtccaatg ccacctagan tntccctgta cacagtgccc ccttgtggca
                                                                      1080
ngttgaccca accttaccag ttggtttttc attttttgtc cctttcccct agatccagaa
                                                                      1140
ataaagtnta agagaagcgc aaaaaaa
                                                                      1167
      <210> 176
      <211> 205
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(205)
      <223> Xaa = Any Amino Acid
      <400> 176
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
                                    10
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
                                25
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
                            4.0
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
                        55
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                    70
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                                    90
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
                                105
Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
                            120
Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
                        135
                                            140
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
                    150
                                        155
Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
                                    170
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
            180
                               185
Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
       195
                            200
                                                205
      <210> 177
      <211> 1119
      <212> DNA
      <213> Homo sapien
      <400> 177
gcgcactcgc agccctggca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc
                                                                       60
gtcctggtgc atccgcagtg ggtgctgtca gccgcacact gtttccagaa ctcctacacc
                                                                      120
atcgggctgg gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag
                                                                      180
gecageetet cegtaeggea eccagagtae aacagaeeet tgetegetaa egaeeteatg
                                                                      240
ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattqct
                                                                      300
```

tegeagtgee etacegeggg gaactettge etegtttetg getggggtet getggegaac 360 gatgctgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc 420 caaccetgge agggttgtac cattteggea acttecagtg caaggaegte etgetgeate 480 ctcactgggt gctcactact gctcactgca tcacccggaa cactgtgatc aactagccag 540 caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt 600 actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc 660 cagttatect cactgaattg agattteetg etteagtgte agceatteee acataattte 720 tgacctacag aggtgaggga tcatatagct cttcaaggat gctggtactc ccctcacaaa 780 ttcatttctc ctgttgtagt gaaaggtgcg ccctctggag cctcccaggg tgggtgtgca 840 ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg 900 ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca 960 accacctcag gactcetgga ttetetgeet agttgagete etgeatgetg ceteettggg 1020 gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc 1080 ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa 1119

<210> 178

<211> 164

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(164)

<223> Xaa = Any Amino Acid

<400> 178

Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp 10 Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu 25 Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val 40 Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu 55 Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser 75 Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly 85 90 Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val 100 105 Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu 120 Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg 135 140 Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Leu Thr Ala Ser 150 155 Pro Gly Thr Leu

<210> 179

<211> 250

<212> DNA

<213> Homo sapien

<400> 179

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ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                        60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct
                                                                       120
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaagcg cttctgctga
                                                                       180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa
                                                                       240
aaaaaaaaa
                                                                       250
      <210> 180
      <211> 202
      <212> DNA
      <213> Homo sapien
      <400> 180
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                        60
teacceagae ecegeceetg ecegtgeece acgetgetge taacgacagt atgatgetta
                                                                       120
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc
                                                                       180
tgatttaaaa aaaaaaaaaa aa
                                                                       202
      <210> 181
      <211> 558
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(558)
      <223> n = A, T, C or G
      <400> 181
tccytttgkt naggtttkkg agacamccck agacctwaan ctgtgtcaca gacttcyngg
                                                                        60
aatgtttagg cagtgctagt aatttcytcg taatgattct gttattactt tcctnattct
                                                                       120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa
                                                                       180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca
                                                                       240
aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaac
                                                                       300
ctactctgtt ccttggctag aaaaaattat aaacaggact ttgttagttt gggaagccaa
                                                                       360
attgataata ttctatgttc taaaagttgg gctatacata aattattaag aaatatggaw
                                                                       420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt
                                                                       480
aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc
                                                                       540
caaaaaaaa aaaaaaaa
                                                                       558
      <210> 182
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(479)
      <223> n = A,T,C or G
      <400> 182
acagggwttk grggatgcta agsccccrga rwtygtttga tccaaccctg gcttwttttc
                                                                       60
agaggggaaa atggggccta gaagttacag mscatytagy tggtgcgmtq qcaccctqq
                                                                      120
cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg
                                                                      180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca
                                                                      240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca
                                                                      300
```

```
tactmttcta agtcctcttc cagcctcact kkgagtcctm cytgggggtt gataggaant
                                                                       360
ntctcttggc tttctcaata aartctctat ycatctcatg tttaatttgg tacgcatara
                                                                       420
awtgstgara aaattaaaat gttctggtty mactttaaaa araaaaaaaa aaaaaaaaa
                                                                       479
      <210> 183
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 183
aggegggage agaagetaaa gecaaageee aagaagagtg geagtgeeag caetggtgee
                                                                        60
agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtggtgg cttcagtgct
                                                                       120
ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt
                                                                       180
gccagcacca gtggcagctc tggtgcctgt ggtttctcct acaagtgaga ttttagatat
                                                                       240
tgttaatcct gccagtcttt ctcttcaagc cagggtgcat cctcagaaac ctactcaaca
                                                                       300
cagcactcta ggcagccact atcaatcaat tgaagttgac actctgcatt aratctattt
                                                                       360
gccatttcaa aaaaaaaaaa aaaa
                                                                       384
      <210> 184
      <211> 496
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(496)
      <223> n = A,T,C or G
      <400> 184
accgaattgg gaccgctggc ttataagcga tcatgtyynt ccrgtatkac ctcaacgagc
                                                                       60
agggagatcg agtctatacg ctgaagaaat ttgacccgat gggacaacag acctgctcag
                                                                      120
cccatcctgc tcggttctcc ccagatgaca aatactctsg acaccgaatc accatcaaga
                                                                      180
aacgcttcaa ggtgctcatg acccagcaac cgcgccctgt cctctgaggg tcccttaaac
                                                                      240
tgatgtcttt tctgccacct gttacccctc ggagactccg taaccaaact cttcggactg
                                                                      300
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg
                                                                      360
attatgcttg tgtgaggcaa tcatggtggc atcacccata aagggaacac atttgacttt
                                                                      420
tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst
                                                                      480
taaaaaaaa aaaaaa
                                                                      496
      <210> 185
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 185
gctggtagcc tatggcgkgg cccacggagg ggctcctgag gccacggrac agtgacttcc
                                                                       60
caagtatcyt gcgcsgcgtc ttctaccgtc cctacctgca gatcttcggg cagattcccc
                                                                      120
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggcttct
                                                                      180
gggcacaccc tcctggggcc caggcgggca cctgcgtctc ccagtatgcc aactggctgg
                                                                      240
tggtgctgct cctcgtcatc ttcctgctcg tggccaacat cctgctggtc aacttgctca
                                                                      300
ttgccatgtt cagttacaca ttcggcaaag tacagggcaa cagcgatctc tactgggaag
                                                                      360
gcgcagcgtt accgcctcat ccgg
                                                                      384
      <210> 186
      <211> 577
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```
<212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(577)
      <223> n = A,T,C or G
      <400> 186
gagttagete etceacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
                                                                         60
tnccategic atactgtagg titgccacca cytectggca tettggggcg gentaatatt
                                                                        120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttccgc
                                                                        180
teggtgtgaa aggateteee agaaggagtg etegatette eccaeaettt tgatgaettt
                                                                        240
attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac
                                                                        300
cagecetate atgeegttga megtgeegaa gareaeegag eettgtgtgg gggkkgaagt
                                                                        360
ctcacccaga ttctgcatta ccagagagec gtggcaaaag acattgacaa actcgcccag
                                                                        420
gtggaaaaag amcamctcct ggargtgctn gccgctcctc gtcmgttggt ggcagcgctw
                                                                        480
tccttttgac acacaaacaa gttaaaggca ttttcagccc ccagaaantt gtcatcatcc
                                                                        540
aagatntcgc acagcactna tccagttggg attaaat
                                                                        577
      <210> 187
      <211> 534
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(534)
      \langle 223 \rangle n = A,T,C or G
      <400> 187
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgstg agaatycatw
                                                                         60
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact
                                                                        120
ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggta
                                                                        180
tgccctattc acacctgtta aaagggcgct aagcattttt gattcaacat ctttttttt
                                                                        240
gacacaagtc cgaaaaaagc aaaagtaaac agttatyaat ttgttagcca attcactttc
                                                                        300
ttcatgggac agagccatyt gatttaaaaa gcaaattgca taatattgag cttygggagc
                                                                        360
tgatatttga gcggaagagt agcctttcta cttcaccaga cacaactccc tttcatattg
                                                                       420
ggatgttnac naaagtwatg tctctwacag atgggatgct tttgtggcaa ttctgttctg
                                                                       480
aggatetece agtttattta ceaettgeae aagaaggegt tttetteete agge
                                                                       534
      <210> 188
      <211> 761
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(761)
      <223> n = A, T, C \text{ or } G
      <400> 188
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                        60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg
                                                                       120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
```

4.4

```
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                       240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg
                                                                       300
ggggacaaag aaaagcaaaa ctgamcataa raaacaatwa cctqqtqaqa arttqcataa
                                                                       360
acagaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt
                                                                       420
gcaaaaaaca tgtacngact tcccgttgag taatgccaag ttgtttttt tatnataaaa
                                                                       480
cttgcccttc attacatgtt tnaaagtggt gtggtgggcc aaaatattga aatgatggaa
                                                                       540
ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac
                                                                       600
atgcttaatt cacaaatgct aatttcatta taaatgtttg ctaaaataca ctttgaacta
                                                                       660
tttttctgtn ttcccagagc tgagatntta gattttatgt agtatnaagt qaaaaantac
                                                                       720
gaaaataata acattgaaga aaaananaaa aaanaaaaaa a
                                                                       761
      <210> 189
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(482)
      <223> n = A,T,C or G
      <400> 189
ttttttttt tttgccgatn ctactatttt attgcaggan gtgggggtgt atgcaccgca
                                                                       60
caccggggct atnagaagca agaaggaagg agggagggca cagccccttg ctgagcaaca
                                                                       120
aagccgcctg ctgccttctc tgtctgtctc ctggtgcagg cacatgggga gaccttcccc
                                                                       180
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag
                                                                       240
tgataggcac aggccacccg gtacagaccc ctcggctcct gacaggtnga tttcgaccag
                                                                       300
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc
                                                                       360
aaatttggct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg
                                                                       420
gttcggccca gctccncgtc caaaaantat tcacccnnct ccnaattgct tgcnggnccc
                                                                       480
                                                                       482
      <210> 190
      <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(471)
      <223> n = A,T,C \text{ or } G
      <400> 190
tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg
                                                                       60
aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atqtnctcca
                                                                      120
aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag
                                                                      180
cgcttttgac atacaatgca caaaaaaaaa agggggggg gaccacatgg attaaaattt
                                                                      240
taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt
                                                                      300
tgaaaaattt catgtatgca atccaaccaa agaacttnat tggtgatcat gantnctcta
                                                                      360
ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacncngt acaaaaanaa
                                                                      420
totgtaattn anttcaacct cogtacngaa aaatnttnnt tatacactco c
                                                                      471
      <210> 191
      <211> 402
      <212> DNA
```

```
<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(402)
      <223> n = A, T, C or G
      <400> 191
gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct
                                                                         60
gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa
                                                                        120
attetteace agteacatet tetaggacet ttttggatte agttagtata agetetteca
                                                                        180
cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg
                                                                        240
ctcgttctct aacaatgtcc tctccttgaa gtatttggct gaacaaccca cctaaagtcc
                                                                        300
ctttgtgcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc
                                                                        360
aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca
                                                                        402
      <210> 192
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (601)
      \langle 223 \rangle n = A,T,C or G
      <400> 192
gageteggat ecaataatet tigtetgagg geageacaea taineagige eatggnaaci
                                                                         60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                        120
atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgyt
                                                                        180
cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc
                                                                        240
acgagacact tgaaaggtgt aacaaagcga ytcttgcatt gctttttgtc cctccggcac
                                                                        300
cagttgtcaa tactaacccg ctggtttgcc tccatcacat ttgtgatctg tagctctgga
                                                                        360
tacateteet gacagtactg aagaacttet tettttgttt caaaagcare tettggtgee
                                                                        420
tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac
                                                                        480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag
                                                                       540
cctcgatgta gccggccagc gccaaggcag gcgccgtgag ccccaccagc agcagaagca
                                                                        600
                                                                        601
      <210> 193
      <211> 608
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(608)
      <223> n = A,T,C or G
      <400> 193
atacagecca nateceacca egaagatgeg ettgttgaet gagaacetga tgeggteact
                                                                        60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt
                                                                       120
cccaacgcag gcagmagcgg gsccggtcaa tgaactccay tcgtggcttg gggtkgacgg
                                                                       180
tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccgac tgtgcgggac
                                                                       240
ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcccag ggccttgccc
                                                                       300
```

ξ.

```
agaacettee geetgttete tggegteace tgeagetget geegetgaca eteggeeteg
                                                                       360
gaccagegga caaacggert tgaacageeg caceteaegg atgeecagtg tgtegegete
                                                                       420
caggammgsc accagegtgt ccaggtcaat gteggtgaag cceteegegg gtratggegt
                                                                       480
ctgcagtgtt tttgtcgatg ttctccaggc acaggctggc cagctgcggt tcatcgaaga
                                                                       540
gregegeetg egrageage argaaggegt tgreggereg eagtrettet teaggaacte
                                                                       600
cacgcaat
                                                                       608
      <210> 194
      <211> 392
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(392)
      <223> n = A,T,C or G
      <400> 194
gaacggctgg accttgcctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt
                                                                       60
ccagtccgag cagccccaga ccgctgccgc ccgaagctaa gcctgcctct ggccttcccc
                                                                       120
tccgcctcaa tgcagaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg
                                                                       180
tttgatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac
                                                                       240
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt
                                                                       300
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg
                                                                       360
aaataaatat agttattaaa ggttgtcant cc
                                                                       392
      <210> 195
      <211> 502
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(502)
      <223> n = A, T, C \text{ or } G
      <400> 195
ccsttkgagg ggtkaggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg
                                                                       60
ccgagctgag gcagatgttc ccacagtgac ccccagagcc stgggstata gtytctgacc
                                                                      120
cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc taqaqqcacc
                                                                      180
aagggaaggc cccattccgg ggstgttccc cgaggaggaa gggaagggc tctgtgtgcc
                                                                      240
ccccasgagg aagaggccct gagtcctggg atcagacacc ccttcacgtg tatccccaca
                                                                      300
caaatgcaag ctcaccaagg tcccctctca gtccccttcc stacaccctg amcggccact
                                                                      360
gscscacacc cacccagage acgccacccg ccatggggar tgtgctcaag gartcgcngg
                                                                      420
gcarcgtgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt
                                                                      480
gctnanaaaa aaaaanaaaa aa
                                                                      502
      <210> 196
      <211> 665
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc_feature
     <222> (1)...(665)
```

360

420

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<223> n = A,T,C or G
      <400> 196
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc
                                                                        60
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt
                                                                       120
wagctgtttk gagttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga
                                                                       180
actwatttat tatcttgtga aaagtataac aatgaaaatt ttgttcatac tgtattkatc
                                                                       240
aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt
                                                                       300
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact
                                                                       360
tcacttggtt attttattgt aaatgartta caaaattctt aatttaagar aatggtatgt
                                                                       420
watatttatt tcattaattt ctttcctkgt ttacgtwaat tttgaaaaga wtgcatgatt
                                                                       480
tcttgacaga aatcgatctt gatgctgtgg aagtagtttg acccacatcc ctatgagttt
                                                                       540
ttcttagaat gtataaaggt tgtagcccat cnaacttcaa agaaaaaaat gaccacatac
                                                                       600
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan
                                                                       660
aaqtq
                                                                       665
      <210> 197
      <211> 492
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(492)
      <223> n = A, T, C or G
      <400> 197
ttttnttttt tttttttgc aggaaggatt ccatttattg tggatgcatt ttcacaatat
                                                                       60
atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg
                                                                       120
aaggcagatt cacagaacat getngtenge ttgcagtttt acctegtana gatnacagag
                                                                       180
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa
                                                                       240
caaaattcta ccctgaaact tactccatcc aaatattgga ataanagtca gcagtgatac
                                                                       300
attetettet gaactttaga ttttetagaa aaatatgtaa tagtgateag gaagagetet
                                                                       360
tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc
                                                                       420
cattleacte ceateacggg agteaatget acetgggaca cttgtatttt gtteatnetg
                                                                       480
ancntggctt aa
                                                                       492
      <210> 198
      <211> 478
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(478)
      <223> n = A, T, C or G
      <400> 198
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa
                                                                       60
tgtntccacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac
                                                                      120
tgagtatatt ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt
                                                                      180
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc aqaaanaaat
                                                                      240
natatatgtc aatcngattt aagatacaaa acagatccta tggtacatan catcntgtag
                                                                      300
```

gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccqta

agcattctag tacctctact ccatggttaa gaatcgtaca cttatgttta catatgtnca

```
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa
                                                                        478
      <210> 199
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(482)
      <223> n = A,T,C \text{ or } G
      <400> 199
agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagaccta
                                                                         60
tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca
                                                                        120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga
                                                                        180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta
                                                                        240
tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga
                                                                        300
aaatttacct ggangaaaag aggctttngg ctggggacca tcccattgaa ccttctctta
                                                                        360
anggacttta agaanaaact accacatgtn tgtngtatcc tggtgccngg ccgtttantg
                                                                        420
aachtngach neaccettht ggaatanant ettgaengen teetgaactt geteetetge
                                                                        480
                                                                        482
      <210> 200
      <211> 270
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(270)
      <223> n = A, T, C or G
      <400> 200
cggccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc
                                                                         60
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc
                                                                        120
aaggetgage tgaegeegea gaggtegtgt caegteecae gaeettgaeg eegtegggga
                                                                        180
cagccggaac agagcccggt gaangcggga ggcctcgggg agcccctcgg gaagggcgc
                                                                        240
ccgagagata cgcaggtgca ggtggccgcc
                                                                       270
      <210> 201
      <211> 419
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(419)
      <223> n = A, T, C \text{ or } G
      <400> 201
ttttttttt ttttggaatc tactgcgagc acagcaggtc agcaacaagt ttattttgca
                                                                        60
gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcgtgg
                                                                       120
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaancgaagc anaantaaca
                                                                       180
tggagtgggt gcaccetece tgtagaacet ggttacnaaa gettggggca gttcacetgg
                                                                       240
```

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```
totgtgaccg toattttott gacatcaatg ttattagaag toaggatato ttttagagag
                                                                    300
tccactgtnt ctggagggag attagggttt cttgccaana tccaancaaa atccacntga
                                                                    360
aaaagttgga tgatncangt acngaatacc ganggcatan ttctcatant cggtggcca
                                                                    419
      <210> 202
      <211> 509
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(509)
      <223> n = A,T,C or G
      <400> 202
60
tggcacttaa tccattttta tttcaaaatg tctacaaant ttnaatncnc cattatacng
                                                                    120
gtnattttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaatnnaa
                                                                    180
tacncncaaa aatcaaaaat atacntntct ttcagcaaac ttngttacat aaattaaaaa
                                                                    240
aatatatacg gctggtgttt tcaaagtaca attatcttaa cactgcaaac atntttnnaa
                                                                    300
ggaactaaaa taaaaaaaaa cactnccgca aaggttaaag ggaacaacaa attcntttta
                                                                    360
caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng
                                                                    420
ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt gggcccaaca
                                                                    480
caatggnaat nccnccncnc tggactagt
                                                                    509
     <210> 203
     <211> 583
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1) ... (583)
     <223> n = A.T.C or G
     <400> 203
ttttttttt tttttttga cccccctctt ataaaaaaca agttaccatt ttattttact
                                                                     60
tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac
                                                                    120
taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt
                                                                    180
gaaaatette tetagetett tigaetgiaa attitigaet etigtaaaac atceaaatte
                                                                    240
attiticity totttaaaat tatotaatot ticcattitt tooctatico aagtoaatti
                                                                    300
gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa
                                                                    360
agggaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc
                                                                    420
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg
                                                                    480
tccattttag tcactaaacg atatcnaaag tgccagaatg caaaaggttt gtgaacattt
                                                                    540
attcaaaagc taatataaga tatttcacat actcatcttt ctg
                                                                    583
     <210> 204
     <211> 589
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(589)
```

480

```
<223> n = A,T,C or G
      <400> 204
60
tttcactctc tagatagggc atgaagaaaa ctcatctttc cagctttaaa ataacaatca
                                                                     120
aatctcttat gctatatcat attttaagtt aaactaatga gtcactggct tatcttctcc
                                                                     180
tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat
                                                                     240
tgagaggttt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccttt
                                                                     300
attttcatgc aaactagaaa ataatgtntt cttttgcata agagaagaga acaatatnag
                                                                     360
cattacaaaa ctgctcaaat tgtttgttaa gnttatccat tataattagt tnggcaggag
                                                                     420
ctaatacaaa tcacatttac ngacnagcaa taataaaact gaagtaccag ttaaatatcc
                                                                     480
aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat
                                                                     540
ttattnagaa tgaattcaca tgttattatt ccntaqccca acacaatqq
                                                                     589
      <210> 205
      <211> 545
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(545)
      <223> n = A,T,C or G
      <400> 205
tttttntttt ttttttcagt aataatcaga acaatattta tttttatatt taaaattcat
                                                                     60
agaaaagtgc cttacattta ataaaagttt gtttctcaaa gtgatcagag gaattagata
                                                                    120
tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat
                                                                    180
ttaagatcat agagcttyta agtgaaaaga taaaatttga cctcagaaac tctgagcatt
                                                                    240
aaaaatccac tattagcaaa taaattacta tggacttctt gctttaattt tgtgatgaat
                                                                    300
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct
                                                                    360
tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt
                                                                    420
aaggggcnga ngaaatgagg aagaaaagaa aaggattacg catactgttc tttctatngg
                                                                    480
aaggattaga tatgtttcct ttgccaatat taaaaaaata ataatgttta ctactagtga
                                                                    540
aaccc
                                                                    545
     <210> 206
     <211> 487
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1) ... (487)
     <223> n = A,T,C or G
     <400> 206
ttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt
                                                                     60
catttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna
                                                                    120
caatttataa atgtaaggtg ccattattga gtanatatat tcctccaaga gtggatgtgt
                                                                    180
cccttctccc accaactaat gaancagcaa cattagttta attttattag tagatnatac
                                                                    240
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag
                                                                    300
ttggtnagaa tgcatcanca atctnacaat caacagcaag atgaagctag gcntgggctt
                                                                    360
tcggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatcct cggtggcaag
                                                                    420
```

aactettega accgetteet caaaggenge tgecacattt gtggentetn ttgeacttgt

```
ttcaaaa
                                                                         487
      <210> 207
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(332)
      \langle 223 \rangle n = A,T,C or G
      <400> 207
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cctttaaaaa
                                                                         60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact
                                                                        120
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana
                                                                        180
atctttgcat gcagaggagg taaaaggtat tggattttca cagaggaana acacagcgca
                                                                        240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg
                                                                        300
aaaagaaggc agcctaggcc ctggggagcc ca
                                                                        332
      <210> 208
      <211> 524
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (524)
      \langle 223 \rangle n = A,T,C or G
      <400> 208
agggcgtggt gcggagggcg ttactgtttt gtctcagtaa caataaatac aaaaagactg
                                                                         60
gttgtgttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat
                                                                        120
tttaaaggac atggagcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac
                                                                        180
tcccgcgtga ttcacattta gcaaccaaca atagctcatg agtccatact tgtaaatact
                                                                        240
tttggcagaa tacttnttga aacttgcaga tgataactaa gatccaagat atttcccaaa
                                                                        300
gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaagtc
                                                                        360
atgageceag acactgaeat caaactaage ceaettagae teeteaceae cagtetgtee
                                                                        420
tgtcatcaga caggaggctg tcaccttgac caaattctca ccagtcaatc atctatccaa
                                                                        480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga
                                                                        524
      <210> 209
      <211> 159
      <212> DNA
      <213> Homo sapien
      <400> 209
gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgctccttg
                                                                         60
tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca
                                                                        120
caaaggactc tcgacccaaa ctgccccaga ccctctcca
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      <210> 210
      <211> 256
      <212> DNA
      <213> Homo sapien
```

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<220>
      <221> misc feature
      <222> (1)...(256)
      <223> n = A,T,C or G
      <400> 210
actccctggc agacaaaggc agaggagaga gctctgttag ttctgtgttg ttgaactgcc
                                                                        60
actgaatttc tttccacttg gactattaca tgccanttga gggactaatg gaaaaacgta
                                                                       120
tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cqqqaqaqt
                                                                       180
ttgcagggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca
                                                                       240
ccaggatgct aaatca
                                                                       256
      <210> 211
      <211> 264
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(264)
      <223> n = A,T,C or G
      <400> 211
acattgtttt tttgagataa agcattgaga gagctctcct taacgtgaca caatggaagg
                                                                       60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                      120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga
                                                                      180
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga
                                                                      240
aaaaaaggag caaatgagaa gcct
                                                                      264
      <210> 212
      <211> 328
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(328)
      <223> n = A,T,C or G
      <400> 212
acccaaaaat ccaatgctga atatttggct tcattattcc canattcttt gattgtcaaa
                                                                       60
ggatttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag
                                                                      120
gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgccag
                                                                      180
ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta
                                                                      240
cccctacnac tctttactct ctgganaggg ccagtggtgg tagctataag cttggccaca
                                                                      300
ttttttttc ctttattcct ttgtcaga
                                                                      328
      <210> 213
      <211> 250
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
```

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<222> (1)...(250)
      <223> n = A,T,C \text{ or } G
      <400> 213
acttatgagc agagcgacat atccnagtgt agactgaata aaactgaatt ctctccagtt
                                                                        60
taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                        120
cattatgcca aagganatat acatttcaat totccaaact tottcctcat tocaagagtt
                                                                        180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatatc tctctnacct
                                                                        240
tctcatcggt
                                                                        250
      <210> 214
      <211> 444
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(444)
      <223> n = A,T,C or G
      <400> 214
acccagaatc caatgctgaa tatttggctt cattattccc agattctttg attgtcaaag
                                                                        60
gatttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg
                                                                       120
tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt
                                                                       180
tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac
                                                                       240
ccctacgact ctttactctc tggagagggc cagtggtggt agctataagc ttggccacat
                                                                       300
ttttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag
                                                                       360
agtgactttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt
                                                                       420
actitgctct ccctaatata cctc
                                                                       444
      <210> 215
      <211> 366
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (366)
      <223> n = A,T,C or G
      <400> 215
acttatgagc agagcgacat atccaagtgt anactgaata aaactgaatt ctctccagtt
                                                                        60
taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                       120
cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt
                                                                       180
ttcaatatti gcatgaacct gctgataagc catgttgaga aacaaatatc tctctgacct
                                                                       240
tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa
                                                                       300
tccaagctgt tttctacact gtaaccaggt ttccaaccaa ggtggaaatc tcctatactt
                                                                       360
ggtgcc
                                                                       366
      <210> 216
      <211> 260
      <212> DNA
      <213> Homo sapien
      <220>
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<221> misc_feature
      <222> (1)...(260)
      <223> n = A,T,C or G
      <400> 216
ctgtataaac agaactccac tgcangaggg agggccgggc caggagaatc tccgcttgtc
                                                                       60
caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc attttttat
                                                                       120
taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa
                                                                       180
atcaaaaatt teetnaagtt nteaagetat eatatataet ntateetgaa aaageaacat
                                                                       240
aattcttcct tccctccttt
                                                                       260
      <210> 217
      <211> 262
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (262)
      \langle 223 \rangle n = A,T,C or G
      <400> 217
acctacgtgg gtaagtttan aaatgttata atttcaggaa naggaacgca tataattgta
                                                                       60
tcttgcctat aattttctat tttaataagg aaatagcaaa ttggggtggg gggaatgtag
                                                                      120
ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt
                                                                      180
atgaataatc tgtatgatta tatgtctcta gagtagattt ataattagcc acttacccta
                                                                      240
atateettea tgettgtaaa gt
                                                                       262
      <210> 218
      <211> 205
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(205)
      <223> n = A,T,C or G
      <400> 218
accaaggtgg tgcattaccg gaantggatc aangacacca tcgtggccaa cccctgagca
                                                                       60
cccctatcaa ctcccttttg tagtaaactt ggaaccttgg aaatgaccag gccaagactc
                                                                      120
aggecteece agttetactg acctttgtee ttangtntna ngteeagggt tgetaggaaa
                                                                      180
anaaatcagc agacacaggt gtaaa
                                                                      205
      <210> 219
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 219
tactgttttg tctcagtaac aataaataca aaaagactgg ttgtgttccg gccccatcca
                                                                       60
accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga
      <210> 220
      <211> 93
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<212> DNA
      <213> Homo sapien
      <400> 220
actagccagc acaaaaggca gggtagcctg aattgctttc tgctctttac atttctttta
                                                                        60
aaataagcat ttagtgctca gtccctactg agt
                                                                        93
      <210> 221
      <211> 167
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(167)
      <223> n = A, T, C or G
      <400> 221
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tettttgece ageetgtgge tetactgtag taagtttetg etgatgagga geeagnatge
                                                                       120
ccccactac cttccctgac gctccccana aatcacccaa cctctgt
                                                                       167
      <210> 222
      <211> 351
      <212> DNA
      <213> Homo sapien
      <400> 222
agggcgtggt gcggagggcg gtactgacct cattagtagg aggatgcatt ctggcacccc
                                                                        60
gttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa
                                                                       120
atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa
                                                                       180
ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt
                                                                       240
taggtgagca tgattagaga gcttgtaggt tgcttttaca tatatctggc atatttgagt
                                                                       300
ctcgtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t
                                                                       351
      <210> 223
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (383)
      <223> n = A,T,C or G
      <400> 223
aaaacaaaca aacaaaaaaa acaattette atteagaaaa attatettag ggaetgatat
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tggtaattat ggtcaattta atwrtrttkt ggggcatttc cttacattgt cttgacaaga
                                                                      120
ttaaaatgtc tgtgccaaaa ttttgtattt tatttggaga cttcttatca aaagtaatgc
                                                                      180
tgccaaagga agtctaagga attagtagtg ttcccmtcac ttgtttggag tgtgctattc
                                                                      240
taaaagattt tgatttcctg gaatgacaat tatattttaa ctttggtggg ggaaanagtt
                                                                      300
ataggaccac agtcttcact tctgatactt gtaaattaat cttttattgc acttgttttg
                                                                      360
accattaagc tatatgttta aaa
                                                                      383
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<210> 224

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<211> 320
      <212> DNA
      <213> Homo sapien
      <400> 224
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                                                                     60
aaaagtttgt gacattgtag tagggagtgt gtacccctta ctccccatca aaaaaaaaat
                                                                     120
ggatacatgg ttaaaggata raagggcaat attttatcat atgttctaaa agagaaggaa
                                                                     180
gagaaaatac tactttctcr aaatggaagc ccttaaaggt gctttgatac tgaaggacac
                                                                     240
aaatgtggcc gtccatcctc ctttaragtt gcatgacttg gacacggtaa ctgttgcagt
                                                                     300
tttaractcm gcattgtgac
                                                                     320
      <210> 225
      <211> 1214
      <212> DNA
      <213> Homo sapien
      <400> 225
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                                                                    120
aacteetaca ecategget gggeetgeac agtettgagg ecgaceaaga geeagggage
                                                                    180
cagatggtgg aggccagcct ctccgtacgg cacccagagt acaacagacc cttgctcgct
                                                                    240
aacgacctca tgctcatcaa gttggacgaa tccgtgtccg agtctgacac catccggagc
                                                                    300
atcagcattg cttcgcagtg ccctaccgcg gggaactctt gcctcgtttc tggctggggt
                                                                    360
ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg tgaacgtgtc ggtggtgtct
                                                                    420
gaggaggtct gcagtaagct ctatgacccg ctgtaccacc ccagcatgtt ctgcgccggc
                                                                    480
ggaggcaag accagaagga ctcctgcaac ggtgactctg gggggcccct gatctgcaac
                                                                    540
gggtacttgc agggccttgt gtctttcgga aaagccccgt gtggccaagt tggcgtgcca
                                                                    600
ggtgtctaca ccaacctctg caaattcact gagtggatag agaaaaccgt ccaggccagt
                                                                    660
taactctggg gactgggaac ccatgaaatt gacccccaaa tacatcctgc ggaaggaatt
                                                                    720 -
caggaatate tgttcccage ceetecteee teaggeccag gagtccagge ecccagecee
                                                                    780
tectecetea aaccaagggt acagateece ageceeteet eceteagace caggagteea
                                                                    840
gacccccag ccctcctcc ctcagaccca ggagtccagc ccctcctccc tcagacccag
                                                                    900
gagtecagae eccecageee etectecete agacecaggg gtecaggeee ecaacecete
                                                                    960
ctccctcaga ctcagaggtc caagccccca acccctcctt ccccagaccc agaggtccag
                                                                   1020
gtcccagccc ctcctccctc agacccagcg gtccaatgcc acctagactc tccctgtaca
                                                                   1080
cagtgccccc ttgtggcacg ttgacccaac cttaccagtt ggtttttcat tttttgtccc
                                                                   1140
1200
aaaaaaaaa aaaa
                                                                   1214
     <210> 226
     <211> 119
     <212> DNA
     <213> Homo sapien
     <400> 226
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                                                                     60
agaacctggc ccagtcataa tcattcatcc tgacagtggc aataatcacg ataaccagt
                                                                    119
     <210> 227
     <211> 818
     <212> DNA
     <213> Homo sapien
     <400> 227
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acaattcata gggacgacca atgaggacag ggaatgaacc cggctctccc ccagccctga
                                                                        60
tttttgctac atatggggtc ccttttcatt ctttgcaaaa acactgggtt ttctgagaac
                                                                       120
acggacggtt cttagcacaa tttgtgaaat ctgtgtaraa ccgggctttg caggggagat
                                                                       180
aattttcctc ctctggagga aaggtggtga ttgacaggca gggagacagt gacaaggcta
                                                                       240
gagaaagcca cgctcggcct tctctgaacc aggatggaac ggcagacccc tgaaaacgaa
                                                                       300
gcttgtcccc ttccaatcag ccacttctga gaacccccat ctaacttcct actggaaaag
                                                                       360
agggcctcct caggagcagt ccaagagttt tcaaagataa cgtgacaact accatctaga
                                                                       420
ggaaagggtg caccctcagc agagaagccg agagcttaac tctggtcgtt tccagagaca
                                                                       480
acctgctggc tgtcttggga tgcgcccagc ctttgagagg ccactacccc atgaacttct
                                                                       540
gccatccact ggacatgaag ctgaggacac tgggcttcaa cactgagttg tcatgagagg
                                                                       600
gacaggetet geceteaage eggetgaggg eageaaceae teteeteece ttteteacge
                                                                       660
aaagccattc ccacaaatcc agaccatacc atgaagcaac gagacccaaa cagtttggct
                                                                       720
caagaggata tgaggactgt ctcagcctgg ctttgggctg acaccatgca cacacacaag
                                                                       780
gtccacttct aggttttcag cctagatggg agtcgtgt
                                                                       818
      <210> 228
      <211> 744
      <212> DNA
      <213> Homo sapien
      <400> 228
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gtcatgacgt ttgacatacc tttggaacga gcctcctcct tggaagatgg aagaccqtqt
                                                                       120
tcgtggccga cctggcctct cctggcctgt ttcttaagat gcggagtcac atttcaatgg
                                                                       180
taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga
                                                                       240
tgctcggtgc acattggggt gctttgggat aaaagattta tgagccaact attctctggc
                                                                       300
accagattct aggccagttt gttccactga agcttttccc acagcagtcc acctctgcag
                                                                       360
gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt
                                                                       420
gagaaggcta ggatgcttgt ctagtgttct tagctgtcac gttggctcct tccaggttgg
                                                                       480
ccagacggtg ttggccactc ccttctaaaa cacaggcgcc ctcctggtga cagtgacccg
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ccgtggtatg ccttggccca ttccagcagt cccagttatg catttcaagt ttggggtttg
                                                                       600
ttcttttcgt taatgttcct ctgtgttgtc agctgtcttc atttcctggg ctaagcagca
                                                                       660
ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt
                                                                       720
cttcactctg aagtagctgg tggt
                                                                       744
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      <211> 300
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      <213> Homo sapien
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cgagtctggg ttttgtctat aaagtttgat ccctcctttt ctcatccaaa tcatgtgaac
                                                                        60
cattacacat cgaaataaaa gaaaggtggc agacttgccc aacgccaggc tgacatgtgc
                                                                       120
tgcagggttg ttgttttta attattattg ttagaaacgt cacccacagt ccctgttaat
                                                                       180
ttgtatgtga cagccaactc tgagaaggtc ctattttcc acctgcagag gatccagtct
                                                                       240
cactaggete etecttgeee teacactgga gteteegeea gtgtgggtge ceactgaeat
                                                                       300
      <210> 230
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 230
cagcagaaca aatacaaata tgaagagtgc aaagatctca taaaatctat gctgaggaat
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gagcgacagt tcaaggagga gaagcttgca gagcagctca agcaagctga ggagctcagg
                                                                       120
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caatataaag teetggttea eacteaggaa egggaaggga gagatgeete eeteteattg gatgaacegg acaagteeca ggggeaggae g	aatgagcatc	tccaggccct	cctcactccg	180 240 300 301		
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<210> 234 <211> 301 <212> DNA <213> Homo sapien			·			
<pre>&lt;400&gt; 234 aggtcctaca catcgagact catccatgat cattttattc atcatgatgc tttcttttgt tcaatttcag caacatactt ctcaaittct cgcctcatga cagcaagttc aatgtttttg ttgatcacca gcttaatggt cagatcatct</pre>	ttcttcttt tcaggattta ccacctgact	cgttttcttc aaatcttgag gaaccacttc	tttttcttt ggattgatct caggagtgcc	60 120 180 240 300		

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t
                                                                        301
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                                                                        60
aattccctca tcttttaggg aatcatttac caggtttgga gaggattcag acagctcagg
                                                                        120
tgettteact aatgtetetg aacttetgte cetetttgtt catggatagt ccaataaata
                                                                       180
atgttatett tgaactgatg etcataggag agaatataag aactetgagt gatateaaca
                                                                       240
ttagggattc aaagaaatat tagatttaag ctcacactgg tca
                                                                       283
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aggtcctcca ccaactgcct gaagcacggt taaaaattggg aagaagtata gtgcagcata
                                                                        60
aatactitta aatcgatcag atttccctaa cccacatgca atcttcttca ccagaagagg
                                                                       120
tcggagcagc atcattaata ccaagcagaa tgcgtaatag ataaatacaa tggtatatag
                                                                       180
tgggtagacg gcttcatgag tacagtgtac tgtggtatcg taatctggac ttgggttgta
                                                                       240
aagcatcgtg taccagtcag aaagcatcaa tactcgacat gaacgaatat aaagaacacc
                                                                       300
                                                                       301
      <210> 237
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 237
cagtggtagt ggtggtggac gtggcgttgg tcgtggtgcc ttttttggtg cccgtcacaa
                                                                        60
actcaatttt tgttcgctcc tttttggcct tttccaattt gtccatctca attttctggg
                                                                       120
ccttggctaa tgcctcatag taggagtcct cagaccagcc atggggatca aacatatcct
                                                                       180
ttgggtagtt ggtgccaagc tcgtcaatgg cacagaatgg atcagcttct cgtaaatcta
                                                                       240
gggttccgaa attctttctt cctttggata atgtagttca tatccattcc ctcctttatc
                                                                       300
۲
                                                                       301
      <210> 238
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 238
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gttcacagtt cagccccctg ctcagaaaac caacgggcca gctaaggaga ggaggaggca
                                                                       120
ccttgagact tccggagtcg aggctctcca gggttcccca gcccatcaat cattttctgc
                                                                       180
accecetgee tgggaageag etecetgggg ggtgggaatg ggtgaetaga agggatttea
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gtgtgggacc cagggtctgt tcttcacagt aggaggtgga agggatgact aatttcttta
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t
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<210> 240 <211> 300 <212> DNA <213> Homo sapien	
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<210> 241 <211> 301 <212> DNA <213> Homo sapien	300
<pre>&lt;400&gt; 241 gaggtctggt gctgaggtct ctgggctagg aagaggagtt ctgtggagct ggaagccaga cctctttgga ggaaactcca gcagctatgt tggtgtctct gagggaatgc aacaaggctg ctcctccatg tattggaaaa ctgcaaactg gactcaactg gaaggaagtg ctgctgccag tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtcttttct tcctcctcct gtcatacggt ctctctcaag catcctttgt tgtcaggggc ctaaaaggga g</pre>	60 120 180 240 300 301
<210> 242 <211> 301 <212> DNA <213> Homo sapien	
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tgacgtgcag tcggactctg tggcccaagg gtatggctct ctcggcatga tgaccagcgt gctggtttgt ccagatggca agacagtaga agcagaggct gcccacggga ctgtaacccg tcactaccgc atgttccaga aaggacagga gacgtccacc aatcccattg cttccatttt	180 240 300 301
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ccagggacct tggaaacagt tgacactgta aggtgcttgc tccccaagac acatcctaaa	180
aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca actgtttgtc ttttgtgtat cttttttaaa ctgtaaagtt caattgtgaa aatgaatatc	240
o o o o o o o o o o o o o o o o o o o	300
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aaggcagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat	120
gttttcaaag agcagagatg caattaaata ttgtttagca tcaaaaaggc cactcaatac	180 240
agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa	300
g	301
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agrigoriori gradaaatta aataadacaq traatroada goottgatar argraccae	180
taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc	240
caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcagaaa c	300
	301
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gtgtcctgtg ttcaggtgcg acacacaatc ctcatgggaa caggatcacc catgcgctgc ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg ggttccttgc	180
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a	300 301

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acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag
                                                                       180
gtacattcca gcctgttggc aactccataa aaacatttca gattttaatc ccqaatttag
                                                                       240
ctaatgagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc
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                                                                       301
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      <211> 301
      <212> DNA
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                                                                       120
ccagggagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc
                                                                       180
catcgtaatg aattattttg aaaattaatt ccaccatcct ttcagattct ggatggaaag
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actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt
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cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac
                                                                       180
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta
                                                                       240
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc
                                                                      300
                                                                       301
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      <211> 301
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      <213> Homo sapien
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                                                                      120
ggcaggggtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtacacct
                                                                      180
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccqqaa
                                                                      240
cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct
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<210> 252 <211> 301

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                                                                        120
 tcattccttt ttcactagga acccattcaa aatataagtc aagaatctta atatcaacaa
                                                                        180
 atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag tacccaaagt
                                                                       240
 tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc
                                                                       300
 а
                                                                       301
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       <211> 301
       <212> DNA
       <213> Homo sapien
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caactaaaaa aaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctccttagct
                                                                       120
tggtctgatt gttttcagac cttaaaatat aaacttgttt cacaagcttt aatccatgtg
                                                                       180
gattttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt
                                                                       240
tccatagtgc ccacagggta ttcctcacat tttctccata ggaaaatgct ttttcccaag
                                                                       300
g
                                                                       301
      <210> 254
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 254
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                                                                       120
ccaaatctct tcatcttacc ctggtggact cctgactgta gaattttttg gttgaaacaa
                                                                      180
gaaaaaaata aagetttgga ettttcaagg ttgettaaca ggtaetgaaa gaetggeete
                                                                      240
acttaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc
                                                                      300
                                                                      301
      <210> 255
      <211> 302
      <212> DNA
      <213> Homo sapien
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attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttggat
                                                                      120
tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtaggggg
                                                                      180
aggaaaaagg actggaggtg gaatctttat aaaaaacaag agtgattgag gcagattgta
                                                                      240
aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac
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                                                                      302
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      <211> 301
     <212> DNA
     <213> Homo sapien
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                                                                         120
acceccaaaa geetggacae ettgageaca cagttatgae caggacagae teatetetat
                                                                         180
aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt
                                                                         240
gtggcctctc ggcctggtta gcaagaacat tcagggtagg cctaagttan tcgtgttagt
                                                                         300
                                                                         301
      <210> 257
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 257
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tececaetta tttttgtett teactatege aggeettaga agaggtetae etgeeteeag
                                                                        120
tottacctag tocagtotac cocotggagt tagaatggcc atcotgaagt gaaaagtaat
                                                                        180
gtcacattac tcccttcagt gatttcttgt agaagtgcca atccctgaat gccaccaaga
                                                                        240
tottaatott cacatottta atottatoto tttgactoot otttacacog gagaaggoto
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                                                                        301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A,T,C or G
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aggggcccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc
                                                                        120
cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactq
                                                                        180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat
                                                                        240
tggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac
                                                                        300
                                                                        301
      <210> 259
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
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      \langle 223 \rangle n = A,T,C or G
      <400> 259
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 gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccagtgggaa
                                                                        120
 gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggtctgt
                                                                        180
 tccagctcac atctcatctg catgcagcac ggaccggatg cgcccactgg gtcttggctt
                                                                        240
 ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcatccttgg ctccaggtgg
                                                                        300
                                                                        301
       <210> 260
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 260
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agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaacaa caggattaac
                                                                       180
tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc
                                                                       240
actgagacat cagtacctgc ccgggcggcc gctcgagccg aattctgcag atatccatca
                                                                       300
C
                                                                       301
      <210> 261
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 261
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                                                                       120
agcaccaact attccataca attcatcagc aggaaataaa ggctcttcag aaggttcaat
                                                                       180
ggtgacatcc aatttettet gataatttag atteeteaca acetteetag ttaagtgaag
                                                                       240
ggcatgatga tcatccaaag cccagtggtc acttactcca gactttctgc aatgaagatc
                                                                       300
                                                                       301
      <210> 262
      <211> 301
      <212> DNA
      <213> Homo sapien
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tgtgagcttc ttgccgcaag tctctcagaa atttaaaaag atgcaaatcc ctgagtcacc
                                                                       120
cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcactctgca tttgtaatga
                                                                       180
gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgccc
                                                                       240
catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat
                                                                       300
      <210> 263
      <211> 301
      <212> DNA
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      <221> misc_feature
      <222> (1)...(301)
      <223> n = A,T,C or G
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tictingial tattiatggt agataggete traceaetry cagatagety generates	180
tadigaciga citicocagia aggototota aggogataagi angaggatoc acaggatito	240
agatyctaag geeccagaga tegittigate caaceetett attiteagag gggaaaatgg	300
g	301
<210> 264	
<211> 301	
<212> DNA	
<213> Homo sapien	
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aatgaatgac tctaaaaaca atatttacat ttaatggttt gtagacaata aaaaaacaag	60
gtggatagat ctagaattgt aacattttaa gaaaaccata scatttgaca gatgagaaag	120
ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac	180
accetteata taaatteact atettggett gaggeactee ataaaatgta teaegtgeat	240
a suppose the decada transfer transfer to a contract the contract transfer to a contract to the contract transfer transfer to the contract transfer	300
	301
<210> 265	• *
<211> 301	
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<213> Homo sapien	
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ttttcagttt gtcacatgt tctctaacaa cacttgccca tttctgtaaa gaatccaaag	180
Cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg	240
c	300
	301
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acaccagate actetiteet etacecacag getigetatg ageaagagae acaaceteet	120
ctcttctgtg ttccagcttc ttttcctgtt cttcccaccc cttaagttct attcctgggg	180
atagagacac caatacccat aacctctctc ctaagcctcc ttataaccca gggtgcacag	240
cacagactee tgacaactgg taaggecaat gaactgggag etcacagetg getgtgeetg	300
•	301
<210> 267	
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aaagagcaca ggccagctca gcctgccctg gccatctaga ctcagcctgg ctccatgggg	60

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atcctcacag gcagcttctg agagcctgat attcctagcc ttgatggtct ggagtaaagc
                                                                       180
ctcattctga ttcctctcct tcttttcttt caagttggct ttcctcacat ccctctgttc
                                                                       240
aattogotto agottgtotg ottragocot catttocaga agottottot otttggcato
                                                                       300
                                                                       301
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      <211> 301
      <212> DNA
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gatettggga gagetggtte ttetaaggag aaggaggaag gacagatgta aetttggate
                                                                       120
tcgaagagga agtctaatgg aagtaattag tcaacggtcc ttgtttagac tcttqqaata
                                                                       180
tgctgggtgg ctcagtgagc ccttttggag aaagcaagta ttattcttaa ggagtaacca
                                                                       240
cttcccattg ttctactttc taccatcatc aattgtatat tatgtattct ttggagaact
                                                                       300
а
                                                                       301
      <210> 269
      <211> 301
      <212> DNA
      <213> Homo sapien
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                                                                       120
atagtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta
                                                                       180
cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta
                                                                       240
tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc
                                                                       300
                                                                       301
      <210> 270
      <211> 301
      <212> DNA
      <213> Homo sapien
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cacaagaata catattcctt ttatttctaa ggagttaaac atagatgtag ctgatgtgga
                                                                       120
gagettgetg gtgeagtgea tattggataa cactatteat ggeegaattg ateaagteaa
                                                                       180
ccaactcctt gaactggatc atcagaagaa gggtggtgca cgatatactg cactagataa
                                                                       240
tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaac
                                                                       300
                                                                       301
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      <211> 301
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                                                                        120
 gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt gggtccaagg
                                                                        180
 tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccatganggt
                                                                        240
 tototoctoc agatganaac tgatcatgcg cocacatttt gggttttata gaagcagtca
                                                                        300
                                                                        301
       <210> 272
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 272
 taaattgcta agccacagat aacaccaatc aaatggaaca aatcactgtc ttcaaatgtc
                                                                         60
ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga
                                                                        120
 tocaataatt cootcatgat gagcaagaaa aattotttgo gcaccootco tgcatcoaca
                                                                        180
gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc
                                                                        240
ctaaggactt ccattgcatc tcctacaata ttttctctac gcaccactag aattaagcag
                                                                        300
g
                                                                        301
       <210> 273
       <211> 301
       <212> DNA
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      <223> n = A, T, C or G
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agagangctg ggacatggat aatcacwtaa tttgctayta tyactttaat ctgactygaa
                                                                       120
gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatttcacc
                                                                       180
ttytttctgt ccagagagag tatcagtgac ananatttma gggtgaamac atgmattggt
                                                                       240
gggactinty titacngagm accordeceg sgegeeeteg makenganti eegesanane
                                                                       300
                                                                       301
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      <400> 274
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aacagtaaat gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa
                                                                       120
tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttgtg gaaaagtcca
                                                                       180
tctaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc
                                                                       240
aattgtgctt cttttgataa gaagctttct tggtcatatc aggaaattcc aganaaagtc
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С
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       <210> 275
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       <212> DNA
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       <223> n = A, T, C or G
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gggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc
                                                                       120
tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag
                                                                       180
tcaagagact cccaggcctc agcgtacctg cccgggcggc cgctcgaagc cgaattctgc
                                                                       240
agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttcgccctat
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      <211> 301
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                                                                       120
taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc
                                                                       180
caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt
                                                                       240
aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat
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                                                                       301
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      <400> 277
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                                                                       120
gaatcatggc actcctgata ctttcccaaa tcaacactct caatgcccca ccctcgtcct
                                                                       180
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga
                                                                       240
gttenetgte gattacatet gaccagtete ettttteega agteenteeg tteaatettg
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                                                                        120
cagtototac tgttattatg cattacotgg gaatttatat aagcoottaa taataatgoo
                                                                        180
aatgaacatc tcatgtgtgc tcacaatgtt ctggcactat tataagtgct tcacaggttt
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tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt
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С
                                                                       301
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      <212> DNA
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                                                                       120
ttagacettt acettecage caccecacag tgettgatat tteagagtea greattggtt
                                                                       180
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac
                                                                       240
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag
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                                                                       301
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      <212> DNA
      <213> Homo sapien
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                                                                       120
tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg
                                                                       180
gtttgatata gtttagggtt ggggttagat taagatctaa attacatcaq qacaaaqaga
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cagactatta actocacagt taattaagga ggtatgttoc atgtttattt qttaaaqcaq
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t.
                                                                       301
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      <211> 301
      <212> DNA
      <213> Homo sapien
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gccgagcaat ccaaatcctg aatgaagggg catcttctga aaaaggagat ctgaatctca
                                                                       120
atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa
                                                                       180
tgtgtagcac actgcgatta cagctaaata acccgtattt gtgtgtcatg tttgcatttc
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g	cacgacggag	cccgcacga	aaacaaagtt	gcagtacctc	300
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<210> 283 <211> 301 <212> DNA <213> Homo sapie	n				
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<210> 284 <211> 301 <212> DNA <213> Homo sapie	n				
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<210> 285 <211> 301 <212> DNA <213> Homo sapie	n				
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:.

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caggaaagca aatgctattt acagacctgc aagccctccc tcaaacnaaa ctatttctgg
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attaaatatg totgacttot tttgaggtca cacgactagg caaatgctat ttacgatctg
                                                                        240
caaaagctgt ttgaagagtc aaagccccca tgtgaacacg atttctggac cctgtaacag
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                                                                        301
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      <212> DNA
      <213> Homo sapien
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atcaaaatgt gtcatgccag taagagatgt tatattcttt tctcatttct tccccaccca
                                                                       180
aaaataagct accatatagc ttataagtct caaatttttg ccttttacta aaatgtgatt
                                                                       240
gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg
                                                                       300
                                                                       301
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      <211> 301
      <212> DNA
      <213> Homo sapien
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cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg
                                                                       120
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accetetgee
                                                                       180
ccgtggttat ctcctcccca gcttggctgc ctcatgttat cacagtattc cattttgttt
                                                                       240
gttgcatgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc
                                                                       300
                                                                       301
      <210> 288
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 288
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agtcaatagg aagacaaatt ccagttccag ctcagtctgg gtatctgcaa agctgcaaaa
                                                                       120
gatetttaaa gacaatttea agagaatatt teettaaagt tggcaatttg gagateatae
                                                                       180
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag
                                                                       240
tctgccttaa ttttggatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa
                                                                      300
                                                                      301
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     <211> 301
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     <213> Homo sapien
     <220>
     <221> misc_feature
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     <223> n = A,T,C or G
     <400> 289
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       <212> DNA
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                                                                        120
 aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt
                                                                        180
 gtgagaattt tttaaaaggc tacttgtata ataacccttg tcatttttaa tgtacctcgg
                                                                        240
 ccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat
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                                                                        301
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                                                                       120
tttaactata gtcacaganc ttaaatattc acattgtttt ctatgtctac tgaaaataag
                                                                       180
ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc
                                                                       240
cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt
                                                                       300
                                                                       301
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      <212> DNA
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cacatttcac tgtgatgtat attgtgttgc aaaaaaaaa gtgtctttgt ttaaaattac
                                                                       120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
                                                                       180
actggtagaa aaacrtctga agagctagtc tatcagcatc tgacaggtga attggatggt
                                                                       240
teteagaace attteaceca gacageetgt ttetateetg tttaataaat tagtttgggt
                                                                       300
tctct
                                                                       305
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                                                                       60
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg
                                                                      120
attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac
                                                                      180
tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt
                                                                      240
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tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg
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 aaggttttga aaaccttgaa ggagaatcat tttgacaaga agtacttaag agtctagaga
                                                                         120
 acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt
                                                                         180
 tocatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggtc
                                                                         240
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                                                                         300
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ggcatctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgccggctg
                                                                        120
tgaagetete agateaatea egggaaggge etggeggtgg tggeeacetg gaaceacet
                                                                        180
gtcctgtctg tttacatttc actaycaggt tttctctggg cattacnatt tgttccccta
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caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctcagcgagg
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gagtttcgcc atgttggcca gctggtctca aactcctgac ctcaagcgac ctgcctgcct
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cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaagatattt
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gctgcattcc acaaggttct cagcctaatg agtttcacta cctgccagtc tcaaaactta
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gtaaagcaag accatgacat tcccccacgg aaatcagagt ttgccccacc gtcttgttac
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tataaagcct gcctctaaca gtccttgctt cttcacacca atcccgagcg catcccccat
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g
                                                                       301
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                                                                       120
gggaactcac aaagaccctc agagctgaga cacccacaac agtgggagct cacaaagacc
                                                                       180
ctcagagetg agacacccac aacagtggga getcacaaag accetcagag etgagacace
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                                                                       120
ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg
                                                                      180
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca
                                                                      240
caggattiga gaigetaagg ceceagagai egittgatee aaccetetta titteagagg
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g
                                                                      301
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tggctaatgg aactaccgct tgcatgttaa aaatggtggt ttgtgaaatg atcataggcc
                                                                      180
agtaacgggt atgttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc
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categatttt atatetgggg tetagaaaag gagttaatet gtttteette ataaatteae
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                                                                      301
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 gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga
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                                                                        120
taaaggagga gaaacagata caaaatctcc aactcagtat taaggtattc tcatgcctag
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aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa
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ttctgggatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag
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                                                                       120
attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt
                                                                       180
cacaccattg gtgagggagg gattaccacc ctggggttat gaagatggtt gaacacccca
                                                                       240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga
                                                                       300
gcaggaggac gcttgcacac catgcaggat gacatggggg atgcgctcgg gattggtgtg
                                                                       360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga
                                                                       420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtgaa
                                                                       480
actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca
                                                                       540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg
                                                                       600
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      <211> 647
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                                                                        120
ggngcctcac agtatagatc tggtagcaaa gaagaagaaa caaacactga tctctttctg
                                                                       180
ccacccctct gaccctttgg aactcctctg accctttaga acaagcctac ctaatatctg
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                                                                       300
cttggctaag atgtgggttc cacattaggt tctgaatatg gggggaaggg tcaatttgct.
                                                                       360
cattttgtgt gtggataaag tcaggatgcc caggggccag agcagggggc tgcttgcttt
                                                                       420
gggaacaatg gctgagcata taaccatagg ttatggggaa caaaacaaca tcaaagtcac
                                                                       480
tgtatcaatt gccatgaaga cttgagggac ctgaatctac cgattcatct taaggcagca
                                                                       540
ggaccagttt gagtggcaac aatgcagcag cagaatcaat ggaaacaaca gaatgattgc
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aatgtccttt tttttctcct gcttctgact tgataaaagg ggaccgt
                                                                       647
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      <211> 460
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                                                                       120
gagcacatct tcagcaagag ggggaaatac tcatcatttt tggccagcag ttgtttgatc
                                                                       180
accaaacate atgecagaat acteageaaa cettettage tettgagaag teaaagteeg
                                                                       240
ggggaattta ttcctggcaa ttttaattgg actccttatg tgagagcagc ggctacccag
                                                                       300
ctggggtggt ggagcgaacc cgtcactagt ggacatgcag tggcagagct cctggtaacc
                                                                       360
acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaaat
                                                                       420
ttgtcttgtt tttgtctttc ggtgtgtaag attcttaagt
                                                                       460
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      <211> 539
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ctaaaggttt taaaatatgt caggattgga agaaggcatg gataaagaac aaagttcagt
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taggaaagag aaacacagaa ggaagagaca caataaaagt cattatgtat tctgtgagaa
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gtcagacagt aagatttgtg ggaaatgggt tggtttgttg tatggtatgt attttagcaa
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taatctttat ggcagagaaa gctaaaatcc tttagcttgc gtgaatgatc acttgctgaa
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ttcctcaagg taggcatgat gaaggaggt ttagaggaga cacagacaca atgaactgac
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atgattatgt cattacatgt atggtagtga tggggatgat aggaaggaag aacttatggc
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                                                                      539
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     <211> 526
     <212> DNA
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                                                                         120
 catttacagc atttaaaatg tgttcagcat gaaatattag ctacagggga agctaaataa
                                                                         180
 attaaacatg gaataaagat ttgtccttaa atataatcta caagaagact ttgatatttg
                                                                        240
 tttttcacaa gtgaagcatt cttataaagt gtcataacct ttttggggaa actatgggaa
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 aaaatgggga aactctgaag ggttttaagt atcttacctg aagctacaga ctccataacc
                                                                        360
 tetetttaca gggageteet geageceeta cagaaatgag tggetgagat tettgattge
                                                                        420
 acagcaagag cttctcatct aaaccctttc cctttttagt atctgtgtat caagtataaa
                                                                        480
 agticiataa acigiagini acitattita atccccaaag cacagi
                                                                        526
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       <211> 500
       <212> DNA
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       <223> n = A,T,C or G
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ccatttetet trecetteca ectgecagtt trgetgacte teaacttgte argagrgraa
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gcattaagga cattatgctt cttcgattct gaagacaggc cctgctcatg gatgactctg
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gcttcttagg aaaatatttt tcttccaaaa tcagtaggaa atctaaactt atcccctctt
                                                                       300
tgcagatgtc tagcagcttc agacatttgg ttaagaaccc atgggaaaaa aaaaaatcct
                                                                       360
tgctaatgtg gtttcctttg taaaccanga ttcttatttg nctggtatag aatatcagct
                                                                       420
ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt
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      <221> misc feature
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      <223> n = A,T,C or G
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ctgctgaaat ggagataatt aacatcacta gaaacagcaa gatgacaata taatgtctaa
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                                                                       240
aaaaggaagc acagagatcc ctgggagaaa tgcccggccg ccatcttggg tcatcgatga
                                                                       300
gcctcgccct gtgcctgntc ccgcttgtga gggaaggaca ttagaaaatg aattgatgtg
                                                                       360
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400- 217	
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                                                                        120
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                                                                        151
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       <220>
       <221> misc_feature
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                                                                       120
agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact
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gcgaacctca cttctagact ttcacggtgg gacgaaacgg gttcagaaac tgccaggggc
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cacacaaatg caatagttgg tcactgcatt tttacctgaa ccaaagctaa acccggtgtt
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gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga
                                                                       420
aaaaacgcac aagagcccct gccctgccct agctgangca c
                                                                       461
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      <211> 400
      <212> DNA
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tctataaatg aatgtgctga agcaaagtgc ccatggtggc ggcgaagaag agaaagatgt
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gttttgtttt ggactetetg tggteeette caatgetgtg ggttteeaac caggggaagg
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gtcccttttg cattgccaag tgccataacc atgagcacta cgctaccatg gttctgcctc
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gaactcctac accateggge tgggcctgca cagtcttgag gccgaccaag agccagggag
                                                                      180
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<212> PRT

<213> Homo sapien

<400> 327

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 1
                 5
                                     10
                                                         15
Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu
                                 25
Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr
                             40
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu
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Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala
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Val Ser Gly Ser Cys Ser
            20
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caccttcatg tgcctgaatg gttgccaggt cagaaaaatc cacccttac gagtgcggct
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gtgccatttc c
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                                                                        120
 agggagacta tacctggctc ttgccctaag tgagaggtct tccctcccgc accaaaaaat
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 agaaaggett tetattteac tggcccaggt agggggaagg agagtaactt tgagtetgtg
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totgagactg actggaccca cocagaccca gggcaaagat acatgttacc atatcatctt
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aggagacact cccagcatgg aggagggttt atcttttcat cctaggtcag gtctacaatg
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ggggaaggtt ttattataga actcccaaca gcccacctca ctcctgccac ccacccgatg
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gccctgcctc c
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cagaagggtc tgaactctac gtgttaccag agaacataat gcaattcatg cattccactt
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gatctgtcca caacaaactt gccctctcat gccttgcctc tcaccatgct ctgctccagg
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tcagcccct tttggcctgt ttgttttgtc aaaaacctaa tctgcttctt gcttttcttg
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122

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addition agencing adjudated coddddaat traffoctaa anathrana	180
- against acycyagage ageggetace caqetqqqqt qqtqqqqca accortagat	240 300
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and a second address of the contract of the co	180
Tytudaggat tecegegeed gegeographat atacttooct trottoone	240
313000000 Cogadialee Codadggcqt Cqqtaqqaaa ffectfqqfq fqfffqta	300
against colacting ingatoridg Edoctrocat aractagete taggers	360
the detection of detailed of the detailed of t	420
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123

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2184

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<212> PRT

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131

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			500				Lys	505					510		_
Asp	ser	A1a 515	rne	меt	GIU	Pro	Arg 520	Tyr	His	Val	Arg	Gly 525	Glu	Asp	Leu

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1400

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Ç.,

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6

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<211> 557
<212> DNA
<213> Homo sapiens
<400> 384
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ggggaagggt cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggt 180
tctgcctcct ggccaagcag gctggtttgc aagaatgaaa tgaatgattc tacagctagg 240
acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300
ctctgtagag agcagcattc ccagggacct tggaaacagt tggcactgta aggtgcttqc 360
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ccttcttatt tatgtgaaca actgtttgtc tttttttgta tcttttttaa actgtaaagt 480
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<212> DNA
<213> Homo sapiens
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teteaaagee atetgetgte ttegagtaeg gacacateat eacteetgea ttgttgatea 180
aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240
tatcagacag gtccagtttc cgcaccaaca cctgctggtt ccctqtcqtq qtctqqatct 300
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gcgaccttgg cccgaaggct ctagcaagga cccaccgacc ccagccgcgg cggcggcgc 180
gcggactttg cccggtgtgt ggggcggagc ggactgcgtg tccgcggacg ggcagcgaag 240
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<211> 537
<212> DNA
<213> Homo sapiens
<400> 387
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tgaaccagga ccggcttctg ggcggctgaa agggcaagg aggcaaggac cccgtctctc 180
ccacggatgg ggagaggca ggaggagacc cagccaagtg ccttttcctc agcactgagg 240
gagggggett gttteeette ceteceggeg acaageteea gggeaggget gteeetetgg 300
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geggeecage acttecteag acacaactte tteetgetge tecagtegtg gggateatea 360
cttacccacc ccccaagttc aagaccaaat cttccagctg cccccttcgt gtttccctgt 420
gtttgctgta gctgggcatg tctccaggaa ccaagaagcc ctcagcctgg tgtagtctcc 480
ctgacccttg ttaattcctt aagtctaaag atgatgaact tcaaaaaaaa aaaaaaa
<210> 388
<211> 520
<212> DNA
<213> Homo sapiens
<400> 388
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tgaggttaaa ccagtttgca ttcccctaat gtggaaaaag taagaggact actcagcact 120
gtttgaagat tgcctcttct acagcttctg agaattgtgt tatttcactt gccaagtgaa 180
ggaccccctc cccaacatgc cccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
ccaggaaact gctacttgtg gacctcacca gagaccagga gggtttggtt agctcacaqq 300
acttecceca ceccagaaga ttageatece atactagaet catacteaac teaactagge 360
tcatactcaa ttgatggtta ttagacaatt ccatttcttt ctggttatta taaacagaaa 420
atctttcctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
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                                                                   520
<210> 389
<211> 365
<212> DNA
<213> Homo sapiens
<400> 389
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gagttaaggc tggatttcag atctgcctgg ttccagccgc agtgtgccct ctgctccccc 120
aacgactttc caaataatct caccagegee ttecagetca ggegteetag aagegtettg 180
aagcotatgg coagctgtot tigtgticco totoaccogo cigtcotoac agctgagact 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
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<210> 390
<211> 221
<212> DNA
<213> Homo sapiens
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<222> (1)...(221)
<223> n = A, T, C or G
<400> 390
tgcctctcca tcctggcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggntt ctcatgggtg tggaacatct ctgcttgcgg tttcaggaag gcctctggct 120
gctctangag tctgancnga ntcgttgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a
<210> 391
<211> 325
<212> DNA
<213> Homo sapiens
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<220>
<221> misc_feature
<222> (1)...(325)
<223> n = A, T, C \text{ or } G
<400> 391
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ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
tagccagggc actgctgcca acagccagtc cnnataccat catgtnaccc ggtgngctct 180
naantingat niccanagee clacecaten tagtietget electacegg niaccageee 240
cactgeccag gaatectaca gecagtacee tgteeegacg tetetaceta ccagtacgat 300
gagacctccg gctactacta tgacc
<210> 392
<211> 277
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(277)
\langle 223 \rangle n = A,T,C or G
<400> 392
atattgttta actccttcct ttatatcttt taacattttc atggngaaag gttcacatct 60
agteteactt nggenagngn etectaettg agtetettee eeggeetgnn eeagtngnaa 120
antaccanga accgncatgn cttaanaacn ncctggtttn tgggttnntc aatgactgca 180
tgcagtgcac caccetgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240
ctgaggatac agcgccgcgt cctgtgttgc tqgggaa
<210> 393
<211> 566
<212> DNA
<213> Homo sapiens
<400> 393
actagtccag tgtggtggaa ttcgcggccg cgtcgacgga caqqtcaqct qtctqqctca 60
gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacqtt 120
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
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gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttggga 300
gggtggtttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360
catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420
cattetetge etgagtttta atttttgtee aaagttattt taatetatae aattaaaage 540
ttttgcctat caaaaaaaaa aaaaaa
                                                                 566
<210> 394
<211> 384
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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<222> (1)...(384)
<223> n = A,T,C or G
<400> 394
gaacatacat gtcccggcac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
tgcaaattng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
gcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc ccaaatacca 180
tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
gaacatccag tttcctgata aggacgatgg gaaccagccc caggaccaaa ttaccatcac 300
agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
tgagcagatg gtttctgagg acgt
<210> 395
<211> 399
<212> DNA
<213> Homo sapiens
<400> 395
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tetgacettg gaetecaaga cetacateaa cageetgget atattagatg atgagecagt 120
tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180
attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
caagttetet tiggaaagee tgggeatete eteactacag acctetgace atgggacqqt 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac
<210> 396
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(403)
<223> n = A,T,C or G
<400> 396
tggagttntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtgagg gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt
<210> 397
<211> 100
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(100)
<223> n = A,T,C or G
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<400> 397
actagtncag tgtggtggaa ttcgcggccg cgtcgaccta naanccatct ctatagcaaa 60
tccatccccg ctcctggttg gtnacagaat gactgacaaa
                                                                100
<210> 398
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(278)
<223> n = A, T, C or G
<400> 398
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ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120
tcactactgt gcctcgacca gtgaggagag ctggaccgac agcgaggtgg actcatcatg 180
ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240
ctatggccgc ttcattangt ggctcaacaa ggagaagg
<210> 399
<211> 298
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(298)
<223> n = A,T,C or G
<400> 399
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ggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcgtgggct 120
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcatgggct 180
ccggcattga gcgcatgggc ccgctgggcc tcgaccacat ggcctccanc attgancgca 240
tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcatggg
<210> 400
<211> 548
<212> DNA
<213> Homo sapiens
<400> 400
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gtacatgtac atgtatgaaa tttccttctc ttaccgaact ctctccacac atcacaaggt 120
tgagtctctt ttttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240
tgcagagggc tagagaatta tttcatacag gctttgaggc cacccatgtc acttatcccg 300
tataccetet caccatecce ttgtctacte tgatgecece aagatgeaac tgggeageta 360
gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420
ctttccagtg atctcctacc atgggccccc ctcctgggat caagcccctc ccaqqcctq 480
tececagece etectgeece ageceacecg ettgeettgg tgeteagece teccattggg 540
agcaggtt
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<210> 401
<211> 355
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A,T,C or G
<400> 401
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tgatgtetee aagtagteea cetteattta aetetttgaa aetgtateat etttgeeaag 120
taagagtggt ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
tataaatgaa tgtgctgaag caaagtgccc atggtggcgg cgaagaagan aaagatgtgt 240
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaaqqqt 300
cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggn tctgc
<210> 402
<211> 407
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(407)
<223> n = A,T,C or G
<400> 402
atggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60
tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300
ttgtggagct tctcccctgc agagagtccc tgatctccca aaatttggtt gagatgtaag 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa
<210> 403
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G
<400> 403
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tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120
tagagaacaa gacctactca gtcatgaaca aaaaggcaga caccaacatg gatctcatgg 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tettaacaac gacegaaace cattatttac ataaacetec atteggtaac catgttgaaa 300
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60

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<211> 225
<212> DNA
<213> Homo sapiens
<400> 404
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attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaaacag 120
acattttcca ctcgtgtttc catagttgtt aagtgtatca gatgtgttgg gcatgtgaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat
<210> 405
<211> 334
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(334)
<223> n = A,T,C or G
gagctgttat actgtgagtt ctactaggaa atcatcaaat ctgagggttg tctggaggac 60
ttcaatacac ctcccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120
tcatccccat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180
ttcccagtgc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240
ctggtgcggt tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc caqcccatqt 300
cactetecae teteteanng tggateceae eect
<210> 406
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(216)
<223> n = A,T,C or G
<400> 406
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gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120
acnaaacaca aatttnatgt tgcacccttg tttctacacc tgtgggttat qacaaaqaca 180
actgccaaag aatnttcaag aaggaggact gccant
<210> 407
<211> 413
<212> DNA
<213> Homo sapiens
<400> 407
gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatqc cttgactcat 60
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180
cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240
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ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300 tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360 tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag <210> 408 <211> 183 <212> DNA <213> Homo sapiens <220> <221> misc\_feature <222> (1)...(183) <223> n = A, T, C or G<400> 408 ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60 tncttaacta gttaatcctt aaagggctan ntaatcctta actagtccct ccattgtgag 120 cattatectt ccagtatten cettetnttt tatttactee tteetggeta eccatgtact 180 <210> 409 <211> 250 <212> DNA <213> Homo sapiens <220> <221> misc\_feature <222> (1)...(250) <223> n = A,T,C or Gcccacgcatg ataagctett tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60 gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctccccta 120 gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180 gcttcccagt gcccccagga cagcgtgggc tatgtttaca gcgcntcctt gctggggggg 240 ggccntatgc 250 <210> 410 <211> 306 <212> DNA <213> Homo sapiens <220> <221> misc\_feature <222> (1)...(306) <223> n = A,T,C or G<400> 410 ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60 agtottgcaa toccatttgc aggatocgto tgtgcacatg cototgtaga gagcagcatt 120 cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaga cacatcctaa 180 aaggtgttgt aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240 nactggttgg ctttttttgn atcttttta aactggaaag ttcaattgng aaaatgaata 300 tentge 306

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<210> 411
<211> 261
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(261)
<223> n = A, T, C or G
<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggngaggcaa a
<210> 412
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
\langle 223 \rangle n = A,T,C or G
<400> 412
gttcaatgtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggagggag 180
ctgggagatt tcactgggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
<210> 413
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(231)
<223> n = A,T,C or G
<400> 413
aactcttaca atccaagtga ctcatctgtg tgcttgaatc ctttccactg tctcatctcc 60
ctcatccaag tttctagtac cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120
aagtttactc tcctcatttg gaacctaaaa actctcttct tcctgggtct gagggctcca 180
agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t
<210> 414
<211> 234
<212> DNA
<213> Homo sapiens
```

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actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60
gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct aqaqaaqqct 120
gtgagccaag gagggagggt cttcctttgg catgggatgg ggatgaagta aggagagga 180
ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca
<210> 415
<211> 217
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(217)
<223> n = A,T,C or G
<400> 415
gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60
caaaacacag accaggtagc aaatctccac tgctctaagg ntctcaccac cactttctca 120
cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180
antggattat aaaaaataac aattaagaaa aataatc
<210> 416
<211> 213
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(213)
<223> n = A, T, C or G
atgcatatnt aaagganact gcctcgcttt tagaagacat ctggnctgct ctctgcatga 60
ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120
cgaatgcaag gtggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180
atattggaac agatggagtc tctactacaa aag
                                                                   213
<210> 417
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(303)
\langle 223 \rangle n = A,T,C or G
<400> 417
nagtottcag goccatcagg gaagttcaca ctggagagaa gtcatacata tgtactqtat 60
gtgggaaagg ctttactctg agttcaaatc ttcaagccca tcagagagtc cacactggag 120
agaagccata caaatgcaat gagtgtggga agagcttcaq gagggattcc cattatcaag 180
ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
agt
                                                                   303
```

```
<210> 418
<211> 328
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(328)
<223> n = A,T,C or G
<400> 418
tttttggcgg tggtggggca gggacgggac angagtctca ctctgttgcc caggctqqaq 60
tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttgt 120
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacaccca gctagtttt 180
gtatttttag tagagacagg gtttcaccat gttggccagg ctggtctcaa actcctnacc 240
tcagnggtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300
aaagtgctan gattacaggc cgtgagcc
<210> 419
<211> 389
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(389)
<223> n = A,T,C or G
<400> 419
cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60
acccctgage catggactgg agectgaaag geagegtaca ecetgeteet gatettgetg 120
cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactgaggc ttqtqcaqqc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacqqt qtgccaqqca 240
ccggttctcc agccaccaac ctcactcgct cccgcaaatg gcacatcagt tcttctaccc 300
taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacq 360
tggcagccac tcnggctgtg tcgacgcgg
<210> 420
<211> 408
<212> DNA
<213> Homo sapiens
<400> 420
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcett agcettgget tettgtttet getttttte tggctagace 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataaqaaaqa 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgctatg acaaacctgg caagcccg
<210> 421
<211> 352
<212> DNA
```

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<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (352)
<223> n = A, T, C or G
<400> 421
gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggtct tttttgggtc cttcttctcc accacnatat acttgcagtc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacaggtg tagaaacaaq 240
ggtgcaacat gaaatttctg tttcgtagca agtgcatgtc tcacaagttg gcangtctgc 300
cacteegagt ttattgggtg tttgttteet ttgagateea tgeattteet gg
                                                                  352
<210> 422
<211> 337
<212> DNA
<213> Homo sapiens
<400> 422
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gcgatagcaa ggtgccggcg atcgcggcgg cgtcaatcct ggccaaggtc agccgtgatc 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggct 240
atccgacacc ggtgcacctg gadgccttgc agcggctggg gccgacgccg attcaccgac 300
gcttcttccg ccggtacggc tggcctatga aaattat
<210> 423
<211> 310
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(310)
<223> n = A,T,C or G
<400> 423
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
tcactgacag aacaggtett ttttgggtee ttetteteea ccaegatata ettgeagtee 180
tccttcttga agattctttg gcagttgtct ttgtcataac ccacaggtgt anaaacaagg 240
gtgcaacatg aaatttctgt ttcgtagcaa gtgcatgtct cacagttgtc aagtctgccc 300
tccgagttta
                                                                   310
<210> 424
<211> 370
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(370)
<223> n = A,T,C or G
```

```
<400> 424
gctcaaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120
cactgacaga acaggtettt tttgggteet tetteteeac cacgatatac ttgcagteet 180
ccttcttgaa gattctttgg cagttgtctt tgtcataacc cacaggtgta qaaacatcct 240
ggttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360
tccgtcgacg
<210> 425
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(216)
<223> n = A, T, C or G
<400> 425
taacaacnca acatcaaggn aaananaaca ggaatggntg acintgcata aatnggccga 120
anattateca ttatnttaag ggttgaette aggntaeage acacagaeaa acatgeecag 180
gaggntntca ggaccgctcg atgtnttntg aggagg
<210> 426
<211> 596
<212> DNA
<213> Homo sapiens
<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcca ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt aqccaqqaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtecegetgg teceatecea ggaeetteea teggegagta eetgggagee egtget
<210> 427
<211> 107
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(107)
<223> n = A, T, C or G
<400> 427
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
```

```
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng
                                                                   107
<210> 428
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(38)
<223> n = A,T,C or G
<400> 428
gaacttccna anaangactt tattcactat tttacatt
                                                                   38
<210> 429
<211> 544
<212> DNA
<213> Homo sapiens
<400> 429
ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagage ggetgeagee etgeggttea gattaaaate egagaattgt atagaegeeg 120
atatccacga actcttgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
gccttccact tcagttacac ctcactcacc atcctctcct gttggttctg tgctgcttca 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccaggtg gtaggagaga 540
ttat
                                                                   544
<210> 430
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (507)
<223> n = A,T,C or G
<400> 430
cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60
gaacactgac acccatcttc caccccgaca ctctgattta attgggctgc agtgagaaca 120
gagcatcaat ttaaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180
ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360
tgtcagtgaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
catteteete tggeetetaa tagteaatga ttgtgtagee atgeetatea gtaaaaaqat 480
ttttgagcaa aaaaaaaaa aaaaaaa
<210> 431
<211> 392
```

```
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(392)
<223> n = A,T,C or G
<400> 431
gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
gcaatgagtc tggcttttac tctgctgttt ct
<210> 432
<211> 387
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(387)
<223> n = A, T, C or G
<400> 432
ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
aaatgcaagg caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg 120
ngtagtccaa gctctcggna gtccagccac tgngaaacat gctcccttta gattaacctc 180
gtggacnetn ttgttgnatt gtetgaactg tagngeeetg tattttgett etgtetgnga 240
attctgttgc ttctggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300
atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
acaacgtata gaacactgga gtccttt
<210> 433
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(281)
\langle 223 \rangle n = A,T,C or G
ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
caggenetat ttgggttgge tggaggget gtggaaaaca tggagagatt ggegetggag 180
ategeogtgg ctatteeten ttgntattae accagngagg ntetetgtnt geccaetggt 240
tnnaaaaccg ntatacaata atgatagaat aggacacaca t
<210> 434
<211> 484
```

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<212> DNA
<213> Homo sapiens
<400> 434
ttttaaaata agcatttagt gctcagtccc tactgagtac tctttctctc ccctcctctg 60
aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120
tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttqc 180
tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
agctagtcta tcagcatctg acaggtgaat tggatgqttc tcaqaaccat ttcacccaqa 300
cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca taacaaaccc 360
tgctccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420
tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480
ttta
<210> 435
<211> 424
<212> DNA
<213> Homo sapiens
<400> 435
gegeegetea gageaggtea etttetgeet tecaegteet eetteaagga ageeecatgt 60
gggtagcttt caatatcgca ggttcttact cctctgcctc tataagctca aacccaccaa 120
cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180
atgggcctgt ggggaggggg caagatagat gagggggagc ggcatggtgc gqqqtqaccc 240
cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300
ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360
gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420
aaac
<210> 436
<211> 667
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A, T, C or G
<400> 436
accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagttttccc aaggtagcta taaaatcctt ataagggtgc 120
agcetettet ggaatteete tgattteaaa gteteaetet caagttettg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggetgee agagtaggat aggatteeag atgetgaeae ettetggggg aaacaggget 300
gccaggtttg tcatagcact catcaaagtc cggtcaacgt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gcccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaaggtg tcaatgggac ttcggtctcc atgccqaaac 540
accaaagtca caaacttcaa ctccttggct agtacacttc ggtctagcca gaaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag
<210> 437
<211> 693
```

```
<212> DNA
<213> Homo sapiens
<400> 437
ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagecag gtaaggaaag etggattgge acactaggae tetaccatae egggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaact tcagacagct ttttcagatc 180
ataaaagata attettagee catgttette teeagageag acetgaaatg acageacage 240
aggtactect etattiteae eestetiget tetactetet ggeagteaga eetgiggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttacccta ggtgtcacta ttggggggac agccagcatc tttagctttc 420
atttgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tectatttet aggeactgag ggetgtgggg tacettgtgg tgccaaaaca gateetgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc
<210> 438
<211> 360
<212> DNA
<213> Homo sapiens
<400> 438
ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcca aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
<210> 439
<211> 431
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(431)
\langle 223 \rangle n = A,T,C or G
<400> 439
gttcctnnta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gcttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t
                                                                   431
<210> 440
<211> 523
<212> DNA
<213> Homo sapiens
```

```
<400> 440
agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcatctga tgagaacaag cta
<210> 441
<211> 430
<212> DNA
<213> Homo sapiens
<400> 441
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcett agcettgget tettgtttet getttttte tggctagace 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag
<210> 442
<211> 362
<212> DNA
<213> Homo sapiens
<400> 442
ctaaggaatt agtagtgttc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcctggaa tgacaattat attttaactt tggtggggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgtttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc
                                                                   362
<210> 443
<211> 624
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(624)
\langle 223 \rangle n = A,T,C or G
<400> 443
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atggtaaaca tccttattat taaagtcaac gctaaaatga atgtgtgtgc atatgctaat 480
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ttcattgcta tagcataaca caaaatttgc ataagtggtg gtcagcaaat ccttgaatgc 180
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<222> (1)...(414)
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93

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Ξ.

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gtttcaacgc attgatgact tctccaagga tcttcctttg gcatcgacca cattcagggg 180
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<222> (1)...(231)
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<211> 231
<212> DNA
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